13th INTERNATIONAL HYPOXIA SYMPOSIUM

February 19–22, 2003
Banff, Alberta, Canada
1. VASCULAR ENDOTHELIAL GROWTH FACTOR IN PATIENTS WITH HIGH-ALTITUDE PULMONARY EDEMA (HAPE).
Michael Hlastala

2. HYPOXIC PULMONARY VASOCONSTRICION (HPV) IS DISTRIBUTED HETEROGENEOUSLY IN THE MAMMALIAN LUNG.

3. HYPoxic PULMONARY VASOCONSTRICTION (HPV) IS DISTRIBUTED HETEROGENEOUSLY IN THE MAMMALIAN LUNG.

4. HIF HAPE AND HILLTOP RATS: A PARADOX UNFOLDING.
Barbara J. Engebretsen, Martha Tissot van Patot, Alan Tucker. Wayne State College, Univ Colorado Health Sciences Center, Colorado State Univ.

Vascular endothelial growth factor (VEGF) is a potent endothelial-cell-specific mitogen and permeability factor, known to be involved in vascular basement membrane destruction and angiogenesis. We hypothesized that VEGF might also play a pathophysiological role in the development of high-altitude pulmonary edema (HAPE) in which the hyper-permeability edema has been evidenced to be one of its pathological features. We measured the concentrations of VEGF in venous serum and bronchoaveolar lavage fluid (BALF) in 9 patients with HAPE and 5 healthy volunteers using enzyme-linked immuno-sorbent assay. We also performed immunohistochemical staining with VEGF antibody in lung tissues of HAPE and controls. The results are shown as in the following table: Values are expressed as the mean ± SE. The Student’s t test was used for the comparisons between the HAPE patients at admission and at recovery; ** and between the HAPE patients at admission and normal controls. # lung materials of HAPE and normal controls came from a autopsied case of HAPE and surgical cases of primary lung cancer, taken from areas distant from the cancerous lesion, respectively. These findings suggest that VEGF may be involved in the lung of HAPE and it appears less likely to have a critical part in the pathogenesis of HAPE, but rather an important role in the repair process for the impaired lung basement membrane in HAPE.
5. PROTECTIVE EFFECT OF FEMALE SEX HORMONES AGAINST PULMONARY HYPERTENSION IN BOLIVIAN HIGH ALTITUDE NATIVES.

Claudio Sartori, Yves Allemandt, Carlos Salinas, Pierre Turini, Armando Rodriguez, Damian Hutter, Sébastien Thalmann, Enrique Vargas, Mercedes Villena, Urs Scherrer, CHUV Lausanne, Insel Spital Berns

There is abundant evidence that female sex hormones have protective effects in the systemic circulation in both animals and humans, but little is known regarding their role in the regulation of the pulmonary circulation. Observations in rats suggest that estrogens may have protective effects against hypoxia-induced pulmonary hypertension. We hypothesized that female sex may confer resistance against pulmonary hypertension in high altitude natives. To test our hypothesis, we performed echocardiographic measurements of the transthoracic pressure gradient as an index of systolic pulmonaryartery pressure in young healthy Bolivians of Aymara ancestry. We studied 82 females and 99 males between 0 and 35 years of age, who were born and living at high altitude (4000 m). To provide additional information, we also measured arterial oxygen saturation and hemoglobin. The main new findings were two-fold. We found a strong direct relationship between age and systolic pulmonary artery pressure in male (r = 0.48, P < 0.001), but not in female (r = 0.16, P > 0.1) high altitude natives. Moreover, starting at the age of 12 years hemoglobin levels were significantly higher in males than in females, and a correlation relationship between hemoglobin and systolic pulmonary artery pressure in male (r = 0.51, P < 0.001), but not female (r = 0.14, P > 0.1) subjects. The gender-related differences in pulmonary artery pressure were not related to differences in arterial oxygen saturation which were comparable in the two groups. These findings provide the first evidence for an age-related increase in pulmonary artery pressure in young healthy male, but not female high-altitude natives. We speculate that female sex may protect against hypoxia-induced pulmonary hypertension in humans, either via decreased hemoglobin concentration and blood viscosity or by favorable effects of female sex hormones on pulmonary endothelial responsiveness to hypoxia.

6. LIVING HIGH—TRAINING LOW: EFFECT ON ERYTHROPOIESIS AND AEROBIC PERFORMANCE IN HIGHLY TRAINED CROSS-COUNTRY SKIERS.

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OBJECTIVES: 1) to verify whether the “living high—training low” method improves red cell mass and maximal aerobic performance, 2) to assess whether markers may predict the individual tolerance for this training method.

METHODS: eleven athletes (6 men, 5 women) performed a 18-day training period (living at 1100m, sleeping either at 1100m (Control, n = 5), VO2max = 59 ± 9ml/min/kg) or in hypoxic rooms (Hypoxia (10h/24h), n = 6, VO2max = 62 ± 4ml/min/kg), the O2 fraction corresponding to 2500m, 3000m and 3500m (3 × 8days). Evaluation was conducted at 1100m, before and 15 days after the end of the training period. Measurements were VO2max (treadmill), time to exhaustion at the velocity at VO2max (Texh), hemoglobin (Hb), hematocrit (Hct), reticulocyte count (RETIC), erythropoietin (EPO), ferritin (Ferrit), serum transferring receptor (sTfR), red cell volume (RCV), CO-rebreathing method. All blood markers (except RCV) were also measured at the end of each altitude stage. Further, before training, all subjects performed a VO2max test at 2500m and spent 3h at rest at 3000m (Hacute). Training load was recorded during the whole study.

RESULTS: Training load during the study was similar between the two groups. Neither VO2max, nor Texh were significantly modified by training, both in control (−2.5% and −14.8%, respectively, n = 5) and in hypoxia groups (−3.9% and −15%, respectively, n = 5). In Hypoxia group, VO2max was found higher (n = 1), unchanged (n = 1) and lower (n = 3), assuming a variation >5%. Training coupled with hypoxic nights increased Hb, Hct, sTfR, whereas no change occurred in Control group. RETIC, VGR and Ferrit were not modified in Hypoxia group. Hacute increased EPO in both groups. However, in Hypoxia group, the changes in aerobic performance (after—before) were related neither to the decrement in VO2max at 2500m, nor to the EPO increase in Hacute. CONCLUSION: The present results indicate that 18 days of “living high—training low” stimulated erythropoiesis. However, two weeks after the end of this protocol, hematomatological parameters had returned to normal values, and aerobic performance was not found increased. This study was supported by grants from the International Olympic Committee and the French Ministry of Sports.

7. ERYTHROPOIETIN PREVENTS DYSFUNCTION OF NITRIC OXIDE SYNTHASE ISOZYME EXPRESSION AFTER SUBARACHNOID HEMORRHAGE IN RATS.

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Erythropoietin (Epo) has been shown to protect against neuronal damage in models of stroke or subarachnoid hemorrhage (SAH). We investigated whether EPO after SAH may mitigate vascular inflammatory effects of SAH, thereby reducing the ischemic insult.

8. NEURAL EPO INCREASES HYPOXIC RESPONSE AND HYPOXIC VENTILATORY ACCLIMATIZATION IN TRANSGENIC MICE.

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Neurally expressed erythropoietin (Epo) has mitogenic and neurotrophic roles protecting against apoptotic and cytotoxic effects of hypoxia. Epo overexpressing transgenic (tg) and wildtype (wt) mice are used to study effects of neuroprotective factors and activation of voltage-gated calcium channels. W added to PC12 cells, Epo is able to increase intracellular Ca2+ (treadmill), time to exhaustion at the velocity at VO2max (Texh), hemoglobin (Hb), hematocrit (Hct), reticulocyte count (RETIC), erythropoietin (EPO), ferritin (Ferrit), serum transferring receptor (sTfR), red cell volume (RCV), CO-rebreathing method. All blood markers (except RCV) were also measured at the end of each altitude stage. Further, before training, all subjects performed a VO2max test at 2500m and spent 3h at rest at 3000m (Hacute). Training load was recorded during the whole study. RESULTS: Training load during the study was similar between the two groups. Neither VO2max, nor Texh were significantly modified by training, both in control (−2.5% and −14.8%, respectively, n = 5) and in hypoxia groups (−3.9% and −15%, respectively, n = 5). In Hypoxia group, VO2max was found higher (n = 1), unchanged (n = 1) and lower (n = 3), assuming a variation >5%. Training coupled with hypoxic nights increased Hb, Hct, sTfR, whereas no change occurred in Control group. RETIC, VGR and Ferrit were not modified in Hypoxia group. Hacute increased EPO in both groups. However, in Hypoxia group, the changes in aerobic performance (after—before) were related neither to the decrement in VO2max at 2500m, nor to the EPO increase in Hacute. CONCLUSION: The present results indicate that 18 days of “living high—training low” stimulated erythropoiesis. However, two weeks after the end of this protocol, hematomatological parameters had returned to normal values, and aerobic performance was not found increased. This study was supported by grants from the International Olympic Committee and the French Ministry of Sports.
9. CHRONIC EXCESSIVE ERYTHROCYTOSIS RESULTS IN SKELETAL MUSCLE DEGENERATION IN MICE OVEREXPRESSIONING ERYTHROPOIETIN.
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Elevated erythropoietin (Epo) plasma level is a common cause of increased hematocrit. The resulting erythrocytosis is assumed to cause higher blood viscosity that puts the cardiovascular system at hemodynamical risk. To follow the physiological consequences of chronic erythrocytosis we generated a transgenic mouse line that due to constitutive overexpression of hEpo (plasma Epo level increases 12-fold) remained with increased hematocrit levels of up to 70% and doubles the blood volume. Despite this excessive erythrocytosis, however, adult transgenic mice did not develop hypertension or thromboembolism. Adap- tational mechanisms involve enhanced expression of endothelial nitric oxide synthase (eNOS) that results in systemic vasodilatation. Importantly, life expectancy of transgenic mice is reduced to about 7-8 months compared to a life span of 18-24 months found in wild-type siblings. Of note, exercise performance of transgenic mice was dramatically reduced. Preliminary analysis of 5-6 months old Epo- mice reveals severe degenerative processes in the skeletal muscle pre- sented as fiber hypertrophy and altered vascular density. At this age first signs of muscular decompensation by overloading are detectable and morphologically represented by i) vacuolization of the muscle, ii) irregular endomysial and perimysial fibrosis with tendency to fiber solidification, iii) focal, scattered fiber atrophy, and finally iv) in some areas a dra- matically decreased capillary density. At 7 months, the hind limb muscle deficiency becomes obvious in most animals without addi- tional loading. Hind limb tremor and toddler increase progressively and the animals suffer from signs of complete paraplegia. The de- velopment of muscle degeneration in an age- and gender-specific manner as well as the cause of the early death are under current in- vestigation. Taken together, our preliminary data provide good evi- dence that long-term, Epo-induced erythrocytosis results in skeletal muscle degeneration.

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11. EXERCISE BEGINS AND ENDS IN THE BRAIN.
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Classically the limit to endurance of exercise is explained in terms of metabolic scope. Cardio-respiratory capacity and muscle fatigue are thought to set the limit. However, a majority of studies on factors limiting endurance exercise discuss issues like VO2max, aerobic enzyme capacity, cardiac output, glycogen stores, etc. In or- der words, in the classic paradigm the limits to endurance are explained with arguments of metabolic nature. How- ever, this paradigm cannot explain the limitation to endur- ance exercise with large muscle groups at altitude when exercise is ended without muscle fatigue and with sub-maximal cardiac output. An at first glance astonishing-ly simple fact provides a basis for an explanation. Any voluntary exercise starts and ends in the brain. Indeed, a conscious decision is necessary to start a voluntary effort, and again, a conscious decision precedes the end of the effort. Based on an original idea by Hill and colleagues (1924) and data from Kayser et al (1994), Noakes et al (2001) recently developed the model of a central govern- nor that integrates input from various sources all related to the exercise. This governor would limit the recruitment of skeletal muscle before the advent of damage to vital organs like the brain and the heart. The proposed govern- nor would also limit exercise at sea level exercise, and may explain early exhaustion in untrained people, early exhaustion during exercise with an expiratory resistance, poor correlations between metabolic markers and marathon running time in elite endurance athletes and many other experimental data.

10. GENETIC MARKER FOR THE ERYTHROPOIETIC RESPONSE TO ALTITUDE.
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Introduction: Altitude training (“Living high-Training low”) improves sea level performance in most endurance athletes. However, there is sub- stantial individual variability in performance enhancement, due at least in part, to different erythropoietic (EPO) responses to altitude. Animal studies suggest that the EPO response to hypoxia may be transcriptionally regulated (Ou et al, 1998), and thereby influenced by genetic mech- anisms. Moreover, many highly polymorphic repeat sequences (dinu- clotide, trinucleotide, or tetranucleotide) have been identified in the human genome within, or closely linked to genes specifically involved in hypoxia sensing and erythropoiesis. We hypothesized that the association of these polymorphisms with divergent phenotypic (in EPO) re- sponses to high altitude would identify those genes that are responsible for individual variability in the erythropoietic response to hypoxia in hu- mans. Methods: EPO concentration was measured in forty-eight competitive runners (32 men, 16 women) before and after 24-hours at a simulated altitude of 2800m. DNA obtained from leukocytes was amplified (PCR) and genotyped for polymorphic markers closely linked to candidate genes including, HIF-1α (transcriptional factor regulating EPO levels), pTEN (a down-regulator of the HIF-1α response), VHL (a posttranslational modu- lator of HIF-1α levels), RENOX (possible oxygen sensor in the kidney), Prolyl Hydroxylase (direct cellular O2 sensor regulating binding of VHL to HIF-1α), EPO gene, and the EPO receptor. High EPO responders (top 17%) and low responders (bottom 23%) were examined for an association between any of these polymorphisms and the specific phenotype. Results: EPO responses ranged from ~41% to 400% of baseline values after 24 hours of simulated altitude. Two different polymorphic markers closely linked to the EPO gene were significantly associated with the phenotype on initial screening. When all athletes were considered, if one of the alle- les of the marker was present (D7S477, homo or heterozygous) the in- crease in EPO was 135±18% versus 78±14% when it was absent (p < 0.02). Conclusion: These data support transcriptional regulation of EPO synthesis in humans. There may exist a specific haplotype of the EPO gene that can be used to predict the erythropoietic response to altitude and thereby response to altitude training. Molecular determinants of the EPO gene regulating these responses remain to be identified.

12. OXYGEN-HEMOGLOBIN AFFINITY AT SEA LEVEL MAY PREDICT ACUTE ILLNESS AT ALTITUDE: THEORY AND SIMULATION.
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Acute mountain sickness carries with it serious health and economic costs. In their pursuit of the mechanisms that produce acute mountain sickness, researchers have overlooked the existence of a possible screening test, a test based on individual variation in cerebral oxygen ex- change at sea level. In this presentation, I highlight the mathematical link between cerebral oxygen exchange at sea level—this is reflected in the magnitude of the oxygen extraction coefficient—and a change in brain blood flow at altitude; this link has been overlooked. A lower oxygen extraction coefficient at sea level can act—at alti- tude—to reduce the capacity of the intracranial compart- ment to accommodate brain swelling, exacerbate in- crease in cell volume, promote the stimulation of angiogenesis, and further cerebral edema, each of which may contribute to acute mountain sickness. In retrospect, it seems obvious that the initial state of cerebral oxygen exchange will impact the cerebral circulatory response to subsequent hypoxia. This deceptively simple notion of- fers us an opportunity to identify beforehand those people likely to develop acute mountain sickness when they travel to altitude.
**Hot Topics in Hypoxia**

13. NASAL LAVAGE VEGF LEVELS DURING ALTITUDE ACCLIMATIZATION.

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Vascular endothelial growth factor (VEGF) is an endothelial-specific mitogen with potent permeability enhancing properties that has been implicated as a potential mediator of capillary leak in high altitude pulmonary (HAPE) and cerebral (HACE) edema. We postulated that nasal lavage VEGF levels would increase with ascent and be highest in subjects that acclimatized poorly or developed severe altitude illness. To test our hypotheses we measured VEGF in the nasal lavage fluid of 15 people (10 male/5 female; 34.7 ± 8.7 years) collected each morning during the acute acclimatization period of a trek in Ladakh, India. Sea level (SL) nasal lavage (NL) samples were collected, the subjects and investigators then flew to Leh, Ladakh (3188 meters). The following two mornings the subjects provided NL samples. On day three the team traveled to an elevation of 5166 meters where they stayed for 4 days and collected morning NL samples. Samples were immediately frozen, stored at −70°C. A ELISA was used to determine NL VEGF levels. Data were analyzed using repeated-measures ANOVA. Multiple pair-wise comparisons were made with the Tukey-Kramer HSD procedure, with significance set at p < 0.05. Sea level NL VEGF (pg/mL) values were 100 ± 52 (mean ± SD) increasing significantly (p < 0.01) to 182 ± 59 on day 1 at 3188 meters then falling to 122 ± 54 on day 2. Again, NL VEGF increased significantly (p < 0.01) to 156 ± 52 at 5166 meters and then fell to 74 ± 38 by day 4. One subject developed HAPE, and another failed to acclimatize, both were transported to Leh for treatment. This study demonstrates the ability to measure VEGF in the nasal lavage fluid. As postulated NL VEGF levels increased with altitude exposure and then fell with acclimatization. The lowest NL VEGF levels were found in the two trekkers who developed severe altitude illness. These findings suggest that an appropriate induction of the hypoxia response proteins and mediators (VEGF included) may be necessary for appropriate altitude acclimatization.

14. EFFECTS OF CHRONIC HYPOBARIC HYPOXIA ON ISOLATED RAT RESPIRATORY AND LIMB SKELETAL MUSCLE CONTRACTILE PROPERTIES.

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Chronic hypoxia occurs in humans in a variety of circumstances including respiratory disease and exposure to altitude and it is known to affect skeletal muscle structure. However, surprisingly little is known about its effects on skeletal muscle function. Thus, the aim of this study was to examine the effects of chronic hypobaric hypoxia on isolated contractile properties of rat respiratory and limb skeletal muscles. Adult male rats were exposed to normoxia (n = 16) or hypobaric hypoxia (n = 16, barometric pressure ≤ 500 mmHg) for 16 weeks. Contractile properties of isolated strips of diaphragm, sternohyoid, extensor digitorum longus (EDL) and soleus muscles were measured in oxygenated Krebs solution in vitro. Isometric twitch and tetanic tension were determined using field stimulation with platinum electrodes. Fatigue was induced by stimulation at 40 Hz with 300msec trains of 0.5Hz for 5 minutes. Chronic hypobaric hypoxia increased specific force development in diaphragm (2.3 ± 0.8 vs. 1.8 ± 0.1 N/cm2 (normoxia vs. hypoxia), sternohyoid (1.7 ± 0.8 vs. 3.1 ± 0.7), EDL (2.5 ± 0.8 vs. 3.8 ± 1.5) and soleus (2.0 ± 0.7 vs. 2.8 ± 0.9) muscles. Furthermore chronic hypoxia increased peak tetanic tension in the sternohyoid (7.9 ± 2.9 vs. 12.9 ± 3.9) and soleus (9.0 ± 4.2 vs. 12.1 ± 3.4) muscles. In addition, chronic hypoxia increased fatigue of the sternohyoid, EDL and soleus muscles but had no significant effect on the diaphragm. In summary, chronic hypobaric hypoxia alters the contractile properties and fatigue characteristics of rat respiratory and limb skeletal muscles. These findings may be relevant to the chronic hypoxia of respiratory disease and exposure to altitude. Supported by Royal College of Surgeons in Ireland, Univ College Dublin, Ireland and The Physiological Society.

15. EFFECT OF EXTRACELLULAR PO2 ON THE FALL IN INTRACELLULAR PO2 IN CONTRACTING SINGLE MYOCYTES.

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This investigation tested the effect of altered extracellular PO2 (PeO2) on the intracellular PO2 (PiO2) response to contractions in single isolated skeletal muscle cells. We hypothesized that as PeO2 increased, thereby increasing the driving force for O2 flux, the fall in PiO2 (proportional to the net increase in VO2) and the specific work of contraction (SWC) would be increased. Single myocytes (n = 12) were dissected from lumbrical muscles of adult female Xenopus laevis and injected with a porphyrin compound for assessment of PiO2 via phosphorescence quenching. For each cell, at PeO2 of ~20 (low), ~40 (moderate) and ~60 (high) Torr, tetanic contractions were induced at a frequency of 0.67 Hz for 2 min with a 5 min recovery between bouts. The PiO2 fall (TDbrutsae@csc.albany.edu.)

16. EUROPEAN GENETIC ADMIXTURE PREDICTS DECREMENT IN AEROBIC PERFORMANCE AT 4338 METERS IN PE- RUVIAN QUECHUA.

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Quechua natives of the high Andes may be genetically adapted to high altitude and thus able to resist decrements in maximal O2 consumption in hypoxia (∆VO2max). This evolutionary hypothesis was tested via the repeated measures of VO2max (sea level versus 4338m) in 30 young male Quechua (18.2 ± 8.7 years) from the Quechua origins. Genetic admixture level (% European genetic influence) was estimated on each individual using a panel of 22 ancestry-informative DNA markers. Genetic admixture explained a significant proportion of the variability in ∆VO2max after controlling for major covariate effects including sea level VO2max and the decrement in arterial O2 saturation (∆SPO2). The genetic effect reflected a main effect of admixture on ∆VO2max (P = 0.041), as well as the interaction between admixture and ∆SPO2 (P = 0.018). The latter means that admixture was predictive of ∆VO2max only in subjects with a large decrease in SPO2 at 4,338 m. In such subjects, ∆VO2max was nearly 22% larger in the highest versus lowest subgroup of European genetic influence (~940 versus ~740 ml/min, respectively; P = 0.031). A non-significant trend for interaction (P = 0.095) was also noted between admixture and the decrease in ventilatory threshold at 4,338 m (∆V(ET呼吸)). Similar to the previous interaction, admixture was predictive of ∆VO2max only in subjects with a large ∆V(ET呼吸). Together, these interactions suggest that the putative genetic effect on ∆VO2max is mediated by a subject’s aerobic fitness level. In particular, genetic effects may be more important (or easier to detect) in very athletic subjects who are more likely to show gas exchange impairment during exercise. In summary, the results of this study are consistent with the evolutionary hypothesis, and point to a better gas exchange system in Quechua as a possible explanation for the admixture effect detected.

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17. INTRACUTANEOUS OXYGEN CONCENTRATION IN NORMAL AND ISCHEMIC SKIN IS INCREASED AFTER INTERMITTENT HYPOXIA TRAINING.

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In earlier studies normobaric intermittent hypoxia training (IHT) was shown to increase survival and cutaneous perfusion of ischemic skin flaps in rats. With this study we investigated the changes of intracutaneous oxygen concentration in normal skin during IHT (course study). Furthermore, we researched the changes of intracutaneous oxygen after rising ischemic skin flaps in IHT-trained and control rats (flap study).

Method: Course study: 16 Wistar rats were randomized into 2 groups of 8 animals each. In the study group the rats were exposed to 20 daily sessions of IHT over 4 weeks with increasing duration and decreasing oxygen content in the breathing air (O2: 10%–9%). The control animals underwent the same training while constantly breathing ambient air (O2: 20.6%). At day 5, 10, 15, 20, 25 continuous intracutaneous measurements were performed during an IHT-session. Flap study: Another set of 16 Wistar rats was trained as described above. After 4 weeks of IHT, caudally based 9 x 3 cm random dorsal skin flaps were elevated. Daily intracutaneous measurements were carried out in the proximal, intermediate and distal part of the flap in IHT and control animals until postoperative day 10.

Results: During the IHT course study, IHT showed to significantly decrease the intracutaneous oxygen concentration during the hypoxic phases. In the intermediate part of the flap the oxygen concentration was more than doubled: IHT vs. control: day 1: 20.1 mmHg vs. 7.8 mmHg; day 3: 14.6 mmHg vs. 6.6 mmHg. Conclusion: IHT leads to an effective systemic adaptation to hypoxia and can be used as a preconditioning technique for skin flaps.

18. INCREASED HYPOXIA-INDUCIBLE TRANSCRIPTION FACTOR ACTIVITY CORRELATES WITH INCREASED ANAEROBIC METABOLISM IN PLACENTAS.

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We have previously presented data indicating that placentas from high altitude pregnancies have reduced activity of hypoxia-inducible transcription factor (HIF). HIF promotes transcription of proteins necessary to rescue tissue from hypoxia, such as vascular endothelial growth factor (VEGF), erythropoietin, and glycolytic enzymes. The surprising finding of reduced HIF activity in high vs. low altitude placental tissue led us to speculate that we may have induced hypoxic/ischemic artifact during collection of the placenta. If the time from placental delivery to placement of tissue in liquid nitrogen was greater at low vs. high altitude, we may have introduced the appearance of reduced HIF activity at high vs. low altitude. Subsequently, we collected placental tissue within 2 minutes of placental delivery and at 5-minute intervals to 25 minutes. Magnetic resonance spectroscopy (MRS) of placental lactate and glucose indicated an increase in anaerobic metabolism up to 11 minutes post-placental delivery. Therefore, we hypothesized that HIF activity would be increased as time from placental delivery is increased, in accordance with an increase in anaerobic metabolism. Methods: Placental samples from the same placentas (n = 4) and time points used in the MRS study were analyzed by electrophoretic mobility shift assay (EMSA). A 22 bp oligonucleotide corresponding to the HIF binding site on VEGF was used to determine HIF binding activity. Results: HIF activity was increased with increasing time from placental delivery. Conclusions: In placenta, HIF activity decreases with increased anaerobic metabolism. Furthermore, results from placental tissue collected within 9 minutes at high and low altitude support our previous findings; high altitude placentas, from successful pregnancies, do have reduced HIF activity as compared to placentas from lower altitude. Could high altitude placentas from successful pregnancies provide insight into the mechanisms of adaptation to hypoxia?

19. THE REGULATION OF BRAIN TISSUE PO2 DURING ACUTE AND CHRONIC HYPOXIA.

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The regulation of brain tissue pO2 during acute and chronic hypoxia Objectives: To determine the capacity of the brain to maintain tissue pO2 (PtO2) during exposure to acute and chronic hypoxia. Methods: Under anesthetized electron paramagnetic resonance (EPR) oximetry to determine the changes in PtO2 in the brain of unanesthetized rats during acute hypoxia, as well as during acclimation to, and recovery from exposure to 1/2 an atmosphere of hypobaric pressure. In one study, animals were acclimated to 1/2 an atmosphere for 28 days, and a control group was maintained under similar conditions while at normobaric pressures. Brain PtO2 was measured in both groups under normobaric, normoxic conditions.

Results: In acute hypoxia, brain PtO2 varies with the inspired oxygen tension. In chronic hypoxia, brain PtO2 was elevated after 3 days in the experimental group, reached a maximum at 7 days and remained constant for the remainder of the 28 days (at more than double the PtO2 of the control group [JCBFM, 2000, v20, p1632]). In a second study, brain PtO2 was measured in rats breathing both 21% and 10% O2 before and after acclimation to 10% O2. The PtO2 in the brain of acclimated animals breathing 10% O2 was not significantly different from the PtO2 of pre-acclimated animals breathing 21% O2. Conclusions: Although the brain does not maintain PtO2 under acute hypoxia, there are adaptive mechanisms initiated by hypoxia which result in acclimation to chronic low oxygen. The brain adapts to chronic hypoxia by returning the tissue to a pre-hypoxic PtO2, indicating that there are O2 sensitive mechanisms (such as HIF-1a) that are capable of sensing PtO2 and initiating a cascade of events which result in the PtO2 returning to normal.
21. DOES MUSCLE VASCULAR MORPHOLOGY ADAPT TO HIGH ALTITUDE?

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High altitude induces adaptive responses to ensure oxygen supply to tissues. Hypoxia-inducible factor 1 (HIF-1) is the transcription factor for many genes that are augmented by hypoxia, including the angiogenic factor VEGF, which modify vascular morphology. In normoxia, HIF-1α subunit activity is inhibited by ubiquitin. In hypoxia, increased HIF-1α mRNA expression and activity by dissociation from ubiquitin has been demonstrated. Aim: We hypothesized that adaptation to altitude would increase mRNA and protein levels of HIF-1α and VEGF and result in increased muscle capillarization. Methods & Results: To test this, muscle biopsies were obtained from 8 Danes at sea level, and after 2 and 8 weeks of exposure to 4,100 m altitude, and from 7 Bolivians of Aymaran ancestry residing at this altitude. Surprisingly, we found no significant differences in HIF-1α or VEGF mRNA levels over time or between subject groups. Correspondingly we found no dynamic change in muscle morphology in the Danes. The main differences were a smaller average fibre area and slightly smaller capillary density in the Bolivians compared to the Danes (Table 1). Conclusion: 8 weeks or lifelong exposure to 4,100 m cause no increase in capillary density in muscle. Table 1. Muscle morphology in Danes at sea level (SL), and after 8 weeks exposure to 4,100 m altitude (CH8), and in Bolivian Aymaras. Values are mean ± SEM.

<table>
<thead>
<tr>
<th>Cap/fiber</th>
<th>Cap/mm²</th>
<th>Mean area</th>
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</tr>
<tr>
<td>CH8</td>
<td>3.6 ± 0.2</td>
<td>578.7 ± 28.0</td>
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<tr>
<td>Aymaras</td>
<td>2.4 ± 0.1*</td>
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Although crude, these data suggest relative changes may be useful for monitoring horses in simulated altitude.

22. METHODS FOR MONITORING HORSES IN A SIMULATED ALTITUDE STALL.

Dawn Howe1, George Swanson1. California State Univ1. dawnhowe@hotmail.com.

Unlike humans, horses have been bred for athletic performance and seem to have adaptive advantages for extreme performance. Horses have a spleen that stores and releases red blood cells when the horse exercises. This release enhances blood oxygen carrying capacity and athletic performance. Can this performance be further enhanced, as it is in humans, if horses experience hypoxic exposure? As a first step to answering this question, we have initiated a pilot study by developing a stall instrumented (Colorado Altitude Training) to simulate an altitude of 12,000 feet and by initiating simple monitoring methods. Our first task was to develop a means for monitoring the equine response to an acute hypoxic exposure. There is no assay available for measuring equine EPO and surface pulse oximeters are not functional for horses. Therefore, we pursued crude methodologies. An equine AeroMask was modified by connecting the two exhalation ports together and to a 49 l plastic bag. An oxygen analyzer could be inserted to measure end-tidal as well as mixed expired oxygen tension. The end-tidal oxygen tension, as an estimate of arterial oxygen tension, together with the equine dissociation curve, yielded an estimate of oxygen saturation. Furthermore, minute ventilation was estimated from bag filling time permitting an estimate of oxygen consumption. We explored the utility of the system, as part of the larger study of performance, a horse was exposed to a simulated altitude of 12,000 feet for 8 hours a day for one month. The average data for normoxia and simulated altitude are shown below. The coefficient of variation over multiple measurements was in the range of 15%.

23. LUNG FUNCTION AFTER RAPID ASCENT TO HIGH ALTITUDE.

Carsten Lundby1, Oliver Senn1, Mikael Sander1, Gerrit van Hall1. Copenhagen Muscle Research Centre1. carsten@cmrc.dk.

High altitude induces adaptive responses to ensure oxygen supply to tissues. Hypoxia-inducible factor 1 (HIF-1) is the transcription factor for many genes that are augmented by hypoxia, including the angiogenic factor VEGF, which modify vascular morphology. In normoxia, HIF-1α subunit activity is inhibited by ubiquitin. In hypoxia, increased HIF-1α mRNA expression and activity by dissociation from ubiquitin has been demonstrated. Aim: We hypothesized that adaptation to altitude would increase mRNA and protein levels of HIF-1α and VEGF and result in increased muscle capillarization. Methods & Results: To test this, muscle biopsies were obtained from 8 Danes at sea level, and after 2 and 8 weeks of exposure to 4,100 m altitude, and from 7 Bolivians of Aymaran ancestry residing at this altitude. Surprisingly, we found no significant differences in HIF-1α or VEGF mRNA levels over time or between subject groups. Correspondingly we found no dynamic change in muscle morphology in the Danes. The main differences were a smaller average fibre area and slightly smaller capillary density in the Bolivians compared to the Danes (Table 1). Conclusion: 8 weeks or lifelong exposure to 4,100 m cause no increase in capillary density in muscle. Table 1. Muscle morphology in Danes at sea level (SL), and after 8 weeks exposure to 4,100 m altitude (CH8), and in Bolivian Aymaras. Values are mean ± SEM.

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<th>Cap/fiber</th>
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Although crude, these data suggest relative changes may be useful for monitoring horses in simulated altitude.

24. FIELD TESTING OF A NEW HIGH-ALTITUDE O2 DELIVERY SYSTEM IN THE BOLIVIAN ANDES.

Alex Vesely1, Ron Somogyi2, T Azami3, David Preiss1, Eitan Prisman1, Len Goodman2, Steve Iscove3, Kyle Pattinson1, Jo Bradwell4, Chris Imray5, Joseph Fisher3. Dept Anesthesia, Toronto General Hospital5, Aircrew Performance Protection Group, DRDC Toronto, Dept Physiology, Queens Univ3, Birmingham Medical Research Expeditionary Society4. alex.vesely@utoronto.ca.

Background: At extreme altitude, bottled O2 is expensive and cumbersome, but necessary. The PaO₂ achievable with simple mask/nasal prongs (NP) or a non-rebreathing mask (e.g. Poisk (P)) is limited by available O₂ flow and high minute ventilations (VE), which dilute inspired O₂. Furthermore, performance is limited by hypacapnia, which reduces cerebral blood flow and increases the affinity of Hb for O₂. We designed a high altitude circuit (HAC) that uses low O₂ flows to provide a constant high FIO₂ and constant PaCO₂ regardless of VE. We compared the PaO₂ attained at 5300 m at resting VE and during hyperventilation using the HAC with that using NP and P. Methods: Five healthy acclimated subjects weighing 73 ± 5 kg breathed room air at rest via the HAC. The O₂ flow required to raise PaO₂ to 100 mmHg (F100) was determined. With O₂ flow set at F100, each subject breathed at rest (5 min) and 3 x resting VE (5 min) on each of the three circuits. Tidal PCO₂ and PaO₂ and VE and Hb saturation were monitored. Results: F100 was 0.8 ± 0.2 L/min (corrected to 1.0 A). At the same O₂ flow (F100), PaO₂ was significantly greater with the HAC than with NP or P (Figure). Hyperventilation did not change PaO₂ with the HAC or P, but improved PaO₂ with NP. Conclusion: In field tests, the HAC demonstrated the highest efficiency of the three O₂ delivery devices. This may allow climbers to carry less O₂ or go farther with a given O₂ supply, and reduce littering. In addition, its ability to control end-tidal PCO₂ may be therapeutically useful for increasing cerebral blood flow and suppressing periodic breathing.
26. THE EFFECT OF SIMULATED ALTITUDE DURING SLEEP ON MODERATE SEVERITY OBSTRUCTIVE SLEEP APNEA.
Keith Burgess¹, Jacky Gehring², Tahnee Kinsman³, Keith Wong⁴, Anthony Rice⁵, Allan Hahn⁶. Univ Sydney¹, Peninsula Private Sleep Laboratory², Australian Institute Sport³, Critical Care Dept Manly Hospital⁴, krburgess@optusnet.com.au.

Field studies in Nepal have shown the replacement of obstructive events (OSA) with central events (CSA) during sleep at high altitudes in normal volunteers (Burgess K et al, Hypoxia 2001). This study was conducted to investigate whether the same effect would be evident in subjects with moderate severity OSA at a simulated altitude of 2750m. Methods: 5 male subjects aged 54+/−6 years (mean ±/−SD), BMI 36.3+/−8.4 and previous mean apnea hypopnea index (AHI) of 32.7+/−10.7/hr were studied on two consecutive nights in the Altitude House at the AIS in Canberra and a third night at "sea level" (100m) in Manly. Two nights breathing ambient air (100m & 600m), the other breathing nitrogen enriched air simulating 2750m. Sleep was monitored by portable PSG equipment with remote monitoring (PS2, Compumedics, Melbourne). Sleep was staged using Rechtschaffen & Kales rules. Respiratory events were scored by the modified Stanford criteria. Results: Obstructive AHI decreased from 25.5+/−14.4/hr at 100m to 17.3+/−9.2 at 600m to 0.5+/−5.8 at 2750m (p = 0.004, ANOVA). While central events increased from 0.4+/−0.5/hr at 100m to 8.1+/−5.8 at 600m to 78.8+/−29.7 at 2750m (p < 0.001). Mean SaO₂ decreased from 94.0+/−1.2% at 100m to 85.0+/−4.0% at 2750m. Conclusion: Overnight exposure to a simulated altitude of 2750m can cause the replacement of documented sea level moderate severity OSA with severe CSA. The pattern was also evident moving between 100m and 600m altitude.

27. HOW ELITE MOUNTAIN CLIMBERS TRAIN TO COPE WITH HYPOXIA.
Sean Egan¹, Shaunna Burke¹. University Ottawa¹. segan@uottawa.ca.

A group of elite climbers (n = 39) were interviewed in order to assess their physical and mental training techniques prior to attempting to summit Mount Everest. Among the climbers were one of the first climbers to summit Everest without oxygen, the oldest climber to summit (64 years), the oldest climber to attempt to summit (71 years), the climber with the most summits and three female climbers. A qualitative method of inquiry (interview) was used to assess the mental techniques used by the climbers. A quantitative method (Questionnaire/interview) was used to collect data on the physical training. The main emphasis of the training was aerobic fitness and ability to regulate one’s breathing, ability to focus, ability to pray and finding inner peace. The physical modalities of training focused mostly on climbing (stairs, hills & mountains); running; cycling; hiking & cross country skiing. The mental training modalities were: meditation; yoga; breathing techniques; music and prayer. The study concluded that the three main factors that trigger mountain sickness in acclimatizing climbers are: The fear factor, inability to relax and inability to breathe correctly. All three are closely linked to one’s physical and mental fitness.

Thursday February 20th 2003

28. DISSOCIATION BETWEEN SKELETAL MUSCLE MICROVASCULAR PO₂ AND HYPOXIA-INDUCED MICROVASCULAR INFLAMMATION.
Norberto Gonzalez¹, Siddarth Shah¹, Julie Allen¹, John Wood¹. Univ Kansas Medical Center¹, ngonzalez@kumc.edu.

On the last meeting we have shown that during decreasing arterial PO₂ oxygen uptake during sub maximal exercise of the working forearm muscles decreased after reaching a PO₂ of 65 Torr while power was unaffected. Lactate release could not compensate for the difference in energy turnover. The aim of the present was to look for differences in recruitment pattern of the exercising muscles. Methods: 8 male subjects performed continuous handgrip exercise with 70% of the maximal workload reached in an incremental test. Contraction frequency was 24 per minutes. Subjects were connected to a closed spirometric system. During exercise oxygen concentration was reduced in the inspired gas by about 3% every 10 minutes down to about 9% (HYP). Contraction velocity and distance were measured continuously. For acid-base state, saturation, lactate and electrolyte determination blood was drawn from a cubital vein of the working forearm. Arterialized blood was drawn from a hyperaemized earlobe and systemic hypoxia produced by breathing 10% O₂. Systemic hypoxia produces an inflammatory response characterized by oxidative stress, and increased leukocyte-endothelial adherence and vascular permeability in mesenteric, brain, and muscle microcirculations. Hypoxia induces hypotension in anesthetized rats, which may result in blood flow-mediated reductions in venular wall shear rate and/or microvascular PO₂ (PmO₂). These experiments were performed to determine the roles of blood flow and PmO₂ on leukocyte adherence to cremaster muscle venules during hypoxia. Cremasteric venules of anesthetized rats were visualized with intravital microscopy. PmO₂ was determined with a phosphorescence decay method. The following experiments were performed: I. Untreated controls; II. Systemic hypoxia: inspired gas: 10% O₂; III. Ischemia: cremaster blood flow restriction; inspired gas: room air; IV. Cremaster hypoxia/systemic normoxia: cremaster equilibrated with 95% N₂, 5% CO₂; inspired gas: room air; V. Cremaster normoxia/systemic hypoxia: cremaster equilibrated with 10% O₂, 5% CO₂; balance N₂, inspired gas: 10% O₂. The following data were obtained after 10 min of each treatment: Leukocyte adherence increased significantly only when PaO₂ was low (groups II and V) even if PmO₂ was elevated (Group V). Muscle hypoxia with normal PaO₂ (groups III and IV) did not elicit leukocyte adherence. Low shear rate did not contribute to leukocyte adherence (Group II vs III). The results suggest that systemic hypoxia elicits the release/generation of a mediator which promotes microvascular inflammation.

Poster Session I

<table>
<thead>
<tr>
<th></th>
<th>I Untreated</th>
<th>II Systemic hypoxia</th>
<th>III Ischemia</th>
<th>IV Cremaster hypoxia</th>
<th>V Cremaster normoxia</th>
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<td><strong>PaO₂, Torr</strong></td>
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<td>33.0±4.0</td>
<td>86.0±4.7</td>
<td>88.8±1.2</td>
<td>34.9±1.2</td>
</tr>
<tr>
<td><strong>PmO₂, Torr</strong></td>
<td>34.8±2.0</td>
<td>6.0±1.7</td>
<td>6.4±1.9</td>
<td>4.2±1.2</td>
<td>63.5±5.5</td>
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<tr>
<td><strong>Venous shear rate, secs</strong></td>
<td>2086±18</td>
<td>126±25</td>
<td>85±22</td>
<td>198±22</td>
<td>822±18</td>
</tr>
<tr>
<td><strong>Adherent leukocytes(100 um)</strong></td>
<td>2.8±0.5</td>
<td>10.0±1.1</td>
<td>4.3±1.1</td>
<td>3.0±0.4</td>
<td>11.5±1.5</td>
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**Poster Session I**
29. SLEEP CHARACTERISTICS IN ACUTE NORMOBARIC HYPOXIA IN RECREATIONAL ATHLETES.

1. Birmingham Medical Centre, 2. Medical School, Univ Liverpool, 3. QinetiQ Ltd., Farnborough, 4. Dept Surgery, Walsgrave Hospital

BACKGROUND: Many athletes routinely use sojourns to altitude to gain the reported benefits such as an improved aerobic capacity (Levine and Stray-Gundersen, 1992). Although sleep at true altitude is well understood, reported effects of normobaric hypoxia upon parameters of sleep (Kinsman et al. 2002). AIM: To evaluate the effects of acute normobaric hypoxia (NH) upon sleep characteristics compared to normobaric normoxia (NN). METHODS: 8 healthy male recre- ational athletes (mean ± sd: age = 34.3 ± 6.87yr; ht = 169.1 ± 6.7cm; wt = 69.3 ± 8.2kg; VO2 max = 56.4 ± 8.3 ml/kg/min) participated in this study. Subjects were investigated over 3 nights. Night 1 was an adaptation night and nights 2 and 3 were either NH (pO2 = 110 mmHg) or NN (pO2 = 159 mmHg) in a double blind, randomized design. Sleep characteristics were measured using actigraphs (Cambridge neurotechnologies, UK—a wrist-watch like device which measures global activity levels), worn continuously for a 2-week period. RESULTS: No significant differences (P > 0.05) were found between NN and NH (Table 1), however, large inter-indi- vidual variation was observed. DISCUSSION: The aim of this study revealed a limited effect of NH upon sleep characteristics; however, large individual differences warrant further investigation. The physiological mechanisms causing these inter-individual differences are unclear.

31. EFFECT OF HARD EXERCISE ON PROTEINURIA AT HIGH ALTITUDE.

Arthur Bradwell1, Stephen Brearey2, Stephen Harris3, Stephen Myers4, Christopher Imray5. The Medical School, Univ Birmingham, 1. Medical School, Univ Liverpool, 2. QinetiQ Ltd, Farnbor- ough, 3. QinetiQ Ltd., Farnborough, 4. Dept Surgery, Walsgrave Hospital

AIM: Despite the prevalence and morbidity associ- ated with high-altitude anorexia-cachexia, the underlying patho- physiology remains elusive. The present study examined whether the peripheral release of catabolic signaling molecules known to influence feeding behavior is subject to redox regulation. METHODS: Following ethical approval, sixteen healthy males participated in a randomized double-blind placebo-controlled trial. Eight subjects were instructed to ingest a combination of water and fat soluble antioxidant vitamins (daily bolus dose of 100mg l-ascorbic acid, 400iu of dl-α-tocopherol acetate and 600mg of l-α-lipoic acid) and the remaining eight subjects ingested a placebo. Supplementation was initiated at sea-level (SL) 7 days prior to departure to India, for 4 days in Delhi and during a 7 day ascent to 4,780m (HA). Resting venous samples obtained at SL and at HA were assayed for metabolic regulators of energy homeostasis and ex-vivo spin trapping with a α-phenyl-tert-butylnitronate (PBN) was combined with electron paramagnetic reso- nance (EPR) spectroscopy for the direct molecular detection of free radicals. Results: Antioxidants decreased the EPR signal intensity of the PBN adduct at HA [SL: 7,369 ± 2,437 vs. HA: 1,548 ± 236 arbitrary units (AU)/Gauss (G), P < 0.05] whereas an increase was observed in the placebo group (6,602 ± 1,813 vs. 10,599 ± 2,729 AU/G, P < 0.05). Antioxidants also prevented the rise in glucagon-like peptide-1 (SL: 25.2 ± 6.4 vs. HA: 29.6 ± 8.2 pmol/L, NS) observed in the placebo group (20.7 ± 9.0 vs. 27.1 ± 13.6, P < 0.05) whereas no selective differences were observed for insulin, glucose, lep-tin or non-esterified fatty acids. Further- more, antioxidants did not influence appetite ratings or alter sub- sequent nutrient intake. Conclusion: The present findings sug- gest that the neuroendocrine modulation of appetite control at high-altitude is not subject to redox regulation.

32. EFFECT OF CAFFEINE INGESTION AT ALTITUDE ON CARDIOVASCULAR AND METABOLIC RE- SPONSES TO AEROBIC EXERCISE.

Arthur Bradwell1, Philip Ainslie2, Mohammed Ghatei3. Univ Glamorgan1, 2. Univ Liverpool, 3. Hammersmith Hospital

Introduction: Despite the prevalence and morbidity associ- ated with high-altitude anorexia-cachexia, the underlying pathophysiology remains elusive. The present study examined whether the peripheral release of catabolic signaling molecules known to influence feeding behavior is subject to redox regulation. METHODS: Following ethical approval, sixteen healthy males participated in a randomized double-blind placebo-controlled trial. Eight subjects were instructed to ingest a combination of water and fat soluble antioxidant vitamins (daily bolus dose of 100mg l-ascorbic acid, 400iu of dl-α-tocopherol acetate and 600mg of l-α-lipoic acid) and the remaining eight subjects ingested a placebo. Supplementation was initiated at sea-level (SL) 7 days prior to departure to India, for 4 days in Delhi and during a 7 day ascent to 4,780m (HA). Resting venous samples obtained at SL and at HA were assayed for metabolic regulators of energy homeostasis and ex-vivo spin trapping with a α-phenyl-tert-butylnitronate (PBN) was combined with electron paramagnetic reso- nance (EPR) spectroscopy for the direct molecular detection of free radicals. Results: Antioxidants decreased the EPR signal intensity of the PBN adduct at HA [SL: 7,369 ± 2,437 vs. HA: 1,548 ± 236 arbitrary units (AU)/Gauss (G), P < 0.05] whereas an increase was observed in the placebo group (6,602 ± 1,813 vs. 10,599 ± 2,729 AU/G, P < 0.05). Antioxidants also prevented the rise in glucagon-like peptide-1 (SL: 25.2 ± 6.4 vs. HA: 29.6 ± 8.2 pmol/L, NS) observed in the placebo group (20.7 ± 9.0 vs. 27.1 ± 13.6, P < 0.05) whereas no selective differences were observed for insulin, glucose, lep-tin or non-esterified fatty acids. Further- more, antioxidants did not influence appetite ratings or alter sub- sequent nutrient intake. Conclusion: The present findings sug- gest that the neuroendocrine modulation of appetite control at high-altitude is not subject to redox regulation.
INTRODUCTION
Anecdotal evidence suggests that when climbing at altitude it is preferable to climb slowly and continuously rather than by using intermittent hard exercise with rests to ‘pause for breath’. METHODS: 6 subjects, 5 male, ages 33–65 Kg/b2 portable metabolic monitor used to measure heart rate, inspired and expired carbon dioxide (CO2), oxygen (O2), respiratory rate and volumes. The course was 75 m vertical ascent from 5260 metres, climbing up a rough mountain path above the Chacaltaya ski station, Bolivia. It took between 6 to 10 minutes to complete. Firstly a slow plood strategy was employed. This involved continuous climbing at a rate at which conversation could be maintained. Ascent was timed. After a two hour rest the experiment was repeated using a ‘rush and rest’ strategy. Subjects were asked to climb quickly, resting as needed, aiming to complete the course in the same time. On each occasion the subjects were allowed to descend the course at their own rate. RESULTS: Subjects felt it took considerably longer to recover following the rush and rest course. Unfortunately there were technical difficulties with the monitor: two data sets were lost no reliable CO2 readings were obtained. (Internal temperature of monitor below working range) No significant difference in oxygen consumption between the two groups, but there was a trend towards a lower oxygen consumption in the rush and rest group. CONCLUSIONS Lower oxygen consumption in “rush and rest” may reflect anaerobic exercise, with oxygen debt being repaid following the period of monitoring. It is planned to repeat this study with a more subjects over a longer course. The monitor needs to be insulated from the cold.

34. OXYGEN CONSUMPTION Whilst CLIMBING MOUNTAINS— IS A SLOW PLOD STRATEGY BETTER THAN RUSH AND REST?
Kyle Pattinson1, Steve Myers2, John Milles3, Chris Imray4. Birmingham Childrens Hospital, Birmingham, UK3, Centre for Human Sciences, Qinetiq, Farnborough, UK3, Good Hope Hospital, Sutton Coldfield, West Midlands, UK3, Univ Hospitals Coventry and Warwickshire NHS trust, Coventry, UK3. kyle999@pobox.com.

CONCLUSIONS
Lower oxygen consumption in “rush and rest” may reflect anaerobic exercise, with oxygen debt being repaid following the period of monitoring. It is planned to repeat this study with a more subjects over a longer course. The monitor needs to be insulated from the cold.
37. ALTITUDE STRATEGIES FOR MAXIMIZING CYCLE SPEED.
George Swanson1. California State Univ1. dswanson@csuchico.edu.
Endurance cycling speed can be enhanced by road racing at higher altitudes. However, a trade-off exists between the reduced drag of altitude and the reduced aerobic power associated with the lower oxygen availability of altitude. These concepts suggest there may be an optimal altitude for maximizing cycling speed. This altitude would balance diminished oxygen availability with diminished drag characteristics to produce a maximum speed. Capelli & di Prampero (Eur. J. Appl. Physiol. 71:469-471, 1995) have determined from basic principles that the optimal one hour endurance altitude is about 16,000 feet for a rode bike. Our approach extends their work by utilizing known physics of air density, a mathematical model of cycling and literature data about the altitude effect on reduced aerobic capacity. This approach results in a mathematical model from which the optimal altitude is determined. For a rode bike, neglecting rolling resistance, our results suggest an optimal altitude of 15,400 feet (similar to Capelli and di Prampero). However, for a recumbent bike, a faring can be used to further reduce drag so that rolling resistance becomes a factor and cannot be neglected. Under these conditions, the model predicts an optimal endurance altitude of about 5,700 feet. Furthermore, when a 30 s anaerobic trust to exhaustion is added to a base line endurance speed so as to maximize the peak velocity, the optimal altitude shifts to about 10,000 feet. Model sensitivity analysis indicates that these altitude estimates have a rather broad confidence interval. Therefore, our results suggest that “mile-high” altitudes maximize endurance speed but “two-mile high” altitudes maximize peak speed. Interestingly, the Colorado Speed Challenge held in Alamosa (1993) at an altitude of about 8000 feet may have been held at an altitude close to optimal and resulted in average 200 meter speeds of near 70 mph.

38. PREDICTION OF PERFORMANCE ON THE ASCENT OF MONT BLANC.
Giorgos Tsianos2, Louise Woolrich3, Martin Watt1, Andrew Peacock3, Tom Atkinson3, Hugh Montgomery3, Ian Watt1, Stanley Grant1. Univ Glasgow, Glasgow Royal Infirmary2, Monklands Hospital, Airdrie3, Western Infirmary, Glasgow4, Univ College, London5. agiosgeorgios@hotmail.com.
The aim of the study was to predict performance on the ascent of Mont Blanc (4,807m) using a number of variables collected at the Gouter Hut (3817m) before and after an attempted ascent on the Mont Blanc summit. Subjects (n = 285) were tested at 3,817m prior to their ascent of Mont Blanc. Subject information included age, dwelling place, altitude experience and an altitude profile (including details of time at altitude in the last 14 days). End tidal CO2, arterial oxygen saturation, heart rate (HR) and respiratory rate (RR) were measured using a Capnograph (Nellcor Patrick NP874). Acute mountain sickness scores were assessed using the Lake Louise scoring system. Logistic regression was used to determine which factors, if any, are predictive of a successful ascent of Mont Blanc. Of the 285 subjects tested, summit information is available for 199 subjects. Of these 199, 184 are known to have reached summit while 15 are known to have failed. The mean (±sd) time to reach the summit from the Gouter Hut was 4.3 ± 2.1 hours. Pre-ascent heart rate and respiratory rate significantly affect the probability of reaching the summit. All subjects with a HR and RR under 84 beats/min and 8 breaths/min respectively, reached the summit. Faster times to the summit are associated with increasing height climbed in the past 14 days. However, the R-Squared (adjusted) is only just over 5.6% and this increases only to 6.6% if one includes the significant additional variable of age. Accordingly, neither of these is even a moderately reasonable predictor of time to the summit regardless of the fact that they are statistically significantly related to it. It was not possible to predict performance on the ascent of Mont Blanc with great precision. A biased sample may have contributed to this limited predictive capability.

39. EFFECTS OF SHORT-TERM MODERATE HYPOXIC EXPOSURE DURING SLEEP ON MAXIMAL AEROBIC CAPACITY AT HIGH ALTITUDE.
taketeru@nifs-k.ac.jp.
Seven male college students were subjected to short-term, intermittent (only during sleep) hypoxic exposure (IHE) in a normobaric hypoxic room set at a moderate altitude (equivalent to an altitude of 2,000 m; O2 16.4%), and the effects of this exposure on maximal aerobic capacity at high altitude (equivalent to an altitude of 4,000 m; O2 12.7%) were examined. Hypoxic exposure was for 4 days. Each day the subjects slept for 7 hours in the hypoxic room, and the effects of IHE on maximal aerobic capacity at high altitude were examined. Results: After this IHE, maximal oxygen uptake (VO2max) and maximal work load at an altitude of 4,000 m significantly increased. Expected volume per minute at the point of VO2max significantly increased after the IHE. However, the red blood cell count and hematocrit level significantly increased after the IHE, and it was surmised that temporary hemodilution had occurred. It can be said from these results that maximal aerobic capacity at high altitude improved even with short-term hypoxic exposure during sleep at a moderate altitude. It is important that hypoxic exposure to moderate (physiologically safe) altitude can improve work capacity at much higher (risks) altitude. And also, it is thought that this improvement was affected by ventilatory adaptation, and that the effects of negative changes in blood properties were small.

40. MAGNITUDE OF DECREASES IN MAXIMAL HEART RATE IN ACUTE AND CHRONIC HYPOXEMIA.
Carsten Lundby1, Mikael Sander1. Copenhagen Muscle Research Centre1. carsten@cmrc.dk.
It is widely accepted that adaptation to hypoxemia is accompanied by decreases in maximal heart rate (mHR). In contrast, recently we reported a linear decrease in mHR during acute exposure to barometric pressures of 518-355 mmHg: mHR(AH) = mHR(SL) - 0.135 ? (530-P(AH)), where AH is acute hypoxia, SL is sea level and PAH is barometric pressure of the acute hypoxic exposure.

Aim: We tested 1) whether this equation would accurately predict decreases in mHR to acute hypoxic exposure at two different levels; and 2) whether mHR decreases progressively during chronic hypoxia of high altitude.

Methods and Results: 12 subjects were studied with continuous ECG during biking with incremental work loads to exhaustion. Protocol 1: mHR was determined during bike-exercise in normoxia (sea level) and during breathing of 12.6% (469 mmHg, n = 8) and 10% oxygen mixtures (394 mmHg, n = 4). The equation predicted decreases in mHR of 8 and 18 beats/min respectively. Experimentally, mHR decreased by 11 + 3.2 and 18 + 5.7 beats/min. In protocol 2, bike-testing were performed during normoxia and acute hypoxia (Copenhagen) and after 2, 4, and 8 weeks of adaptation to high altitude. We tested 1) whether this equation would accurately predict decreases in mHR to acute hypoxic exposure at two different levels; and 2) whether mHR decreases progressively during chronic hypoxia of high altitude.

Conclusions: The main findings were two fold. First, the equation reliably predicts decreases in mHR during acute hypoxia exposure to simulated altitudes above 3,000 m. Second, there is no clear time-dependent further decrease in mHR during prolonged stay at an altitude of 4,100 m. However, in previous studies further decreases in mHR were identified during adaptation to altitudes above 5,000 m.
MAXIMAL OXYGEN UPTAKE AT ALTITUDE USING A BREATH-BY-BREATH METABOLIC ANALYSER AND SUPINE CYCLE ERGOMETER.

Steve Myers1, Steve Harris2, Ian Chesner3, Arthur Bradwell2. QinetiQ Centre for Human Sciences1, QinetiQ2, Birmingham Heartlands hospital3, Dept. Immunology Medical School Univ Birmingham3, steve.myers@ntlworld.com.

INTRODUCTION: The aim of this study was to take direct measurement of maximal oxygen uptake at altitudes of 5260m using a commercially-available breath-by-breath metabolic analyser and a purpose-built, compact, light-weight ergometer that allows exercise in the supine position. METHODS: Eight men and one woman (mean (±SD): age 47.3 (11.8) years; height 181.1 (5.1) cm; body mass 82.7 (10.4) kg). VO2max was measured at 4 locations: Birmingham (BM), UK (96m) and La Paz (LP) (3610m), Refugio Huayna Potosi (RP) (4750m), Bolivia. Subjects exercised on a purpose-built, supine, cycle ergometer (Figure 1) that allowed the head to remain still to permit simultaneous measurements of expired gas and cerebral oxygenation and blood flow. Oxygen uptake was measured using a portable, breath-by-breath O2/CO2 analyser (Cosmed K4b2). Following a 5-minute cycle warm-up, subjects completed an incremental (20 watt per minute) VO2max test to volitional exhaustion. Data were analysed using a repeated measure ANOVA, and differences were located using Fisher’s Protected Least Significance Difference post hoc test. The alpha level was set at 0.05. RESULTS: The cycle ergometer proved to be robust, reliable and easy to use. During the expedition we experienced no failures of the ergometer during 72 maximal and sub-maximal exercise tests. Maximal oxygen uptake (Figure) decreased with altitude. CONCLUSION: The use of reliable and portable equipment to measure the rate of oxygen uptake during standardised maximal and sub-maximal exercise tests will extend the capability for making field measurements of cardio-respiratory function. The VO2max values are comparable with those found in other studies confirming the K4b2 as a reliable tool for use in high altitude research.

Changes in maximal oxygen uptake (CH lower than BM p < 0.05)

SLEEP STRUCTURE AND PERIODIC BREATHING IN TIBETANS AND HAN AT 5000 M.

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Tibetans are the oldest population living permanently at high altitude. They possess several adaptations to low oxygen pressure that allow them to maintain a better sleep structure and oxygenation during sleep at high altitude than newcomers from lower altitudes acclimatized to living at high altitude. We studied 8 healthy young Tibetans, aged 26 ± 7 years, and 6 healthy young Han aged 30.5 ± 4 years. All subjects were living on the Tibetan plateau at an altitude of around 4000 meters. Investigations were performed in Xining at an altitude of 2261 m, PB = 581 mmHg. Two full polysomnographies (PSG) were performed in a hypobaric chamber, one at the ambient altitude, the second during acute exposure to the simulated altitude of 5000 m (PB = 405 mmHg). Both PSG were done on the same night using split night design. At 2261 m no differences in sleep structure, breathing pattern during sleep or oxygenation were found, except a higher number of arousals and awakenings in Han as compared to Tibetans (2002). At 5000 m a different sleep pattern (P = 0.002), shorter stage 1 non-REM sleep (P < 0.001) and longer stage 2 non-REM sleep than Han (P < 0.001). Tibetans showed a trend to have more periodic breathing and higher mean arterial blood saturation than Han during exposure to the simulated altitude of 5000 m.

ANDEAN AND HAN HAVE GREATER UTERINE ARTERY (UTA) ENLARGEMENT DURING PREGNANCY THAN EUROPEAN RESIDENTS OF 3600 M.

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Objectives: To determine whether Andean women weigh less at high altitude but multigenerational high-altitude residents are protected from this birth weight decline (Moore HAMB 2001). Objective: We asked if higher arterial oxygenation and/or UTA blood flow raised uteroplacental O2 delivery in multigenerational Andean women during pregnancy compared with European counterparts. METHODS: Subjects were 45 women of Andean (n = 50, And) or European (n = 11, Eur) ancestry who had resided in La Paz, Bolivia since birth (And) or the past 4 years (Eur). Ancestry was confirmed by genetic markers. Studies were performed at weeks 20, 30, 36 of pregnancy and again 4-6 months postpartum as an index of the non-pregnant state. Arterial O2 saturation (SaO2) was measured by oximetry, hemoglobin concentration by spectrophotometry, and UTA blood flow calculated from vessel diameter and flow velocity obtained by Doppler ultrasound (ATI, 3000 and an investigational Doppler). Results: SaO2 rose during pregnancy similarly in And and Eur subjects (table). Hemoglobin concentration was modestly higher in Eur than And women near term such that measured arterial O2 content was slightly higher in the Eur group. Uterine artery (UTA) diameter increased with pregnancy but the increase was substantially greater (p < 0.01) in the And than Eur women. Flow velocities did not differ between groups although And women had greater velocities in a given vessel diameter than And women. Consequently, And women tended to have greater UTA blood flow (348 ± 198 ml/min vs. 275 ± 126 ml/min; p = 0.04) than Eur women. Conclusion: Greater UTA enlargement but not SaO2 rise underaromatize 02 delivery and likely protect against altitude associated reductions in fetal growth in Andean high-altitude residents, perhaps as the result of natural selection acting on genes influencing these responses. (NIH TW01188, HL60131).

PROLONGED POSTNATAL CARDIOPULMONARY TRANSITION AT 3700-4000M.

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Objective: High-altitude hypoxia influences postnatal changes in the pulmonary circulation. We documented persistence of fetal circulatory patterns and measures of pulmonary artery pressure (PAP) among healthy and sick, native and non-native infants born at 3700-4000m in La Paz, Bolivia. METHODS: Echocardiography on 22 infants at 2 weeks, 1, 3, and 6 months estimated PAP of healthy infants was elevated in the first months, but by 6 months reached norms for childhood at 3700m. Six ill infants experienced acute pulmonary hypertension, surfactant deficiency, and/or retained fetal lung fluid at birth. One premature infant developed symptomatic pulmonary hypertension at 3 months. Conclusion: Postnatal changes in the pulmonary circulation occur slowly at high altitude, with greater vulnerability to incomplete or disrupted transition.
UTERINE ARTERY BLOOD FLOW DURING PREGNANCY IN HIGH-ALTITUDE AYMARA WOMEN.


Background: Birth weight falls with increasing altitude as the result of intrauterine growth restriction (IUGR) likely due, in turn, to low: uterine artery (UA) blood flow. The adaptation-associate birth weight decline is least in the longest resident (in generations) groups, suggesting that adaptations may have occurred that raise uteroplacental blood flow to near sea-level values (Moore et al. HAMB 2001). Study Objective: Determine factors responsible for raising UA blood flow in Andean pregnant women, and whether the values near term resemble those of low-altitude residents. Methods: Measurements of the vessel diameters and blood flow velocities (averaged throughout the cardiac cycle) were made for the UA, common iliac (CI), and external iliac (EI) arteries at 20, 30, and 36 weeks of pregnancy and 3 months postpartum to measure the non-pregnant state, using Doppler ultrasound (ATL 3000 and an investigational Doppler Velocimeter). Results: UA volumetric flow increased as a result of an early enlargement of UA diameter with a continued, progressive rise in flow velocity. There was a corresponding rise in CI flow, which was increasingly directed to the UA (see figure). The increase in CI flow was due primarily to an increase in vessel diameter. The near term UA volumetric flow appears similar to that of low-altitude residents (wk 36 value = 333 mL/min, Palmer OB Gyn 1992), consistent with our hypothesis. This suggests that selection may have acted on the factors responsible for raising UA diameter and flow velocity. (HL60131, TW01188)

CARDIORESPIRATORY RESPONSES OF CHILDREN IN PUTRE AT 3500 M. A COMPARISON BETWEEN AYMARAS AND NO-AYMARAS.

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Objectives: The study describes cardiorespiratory responses and acute mountain sickness (AMS) in a population of children that upon to Arica to Putre and 10 Children no Aymaras (4.3 ± 1.6 years) that born in Arica and live in Putre and 20 Aymaras (4.2 ± 1.6 years) children that born in Arica and live in Putre. Methods: We evaluated Cardiorespiratory measurements included heart rate and oxygen saturation and AMS symptoms only in children that arrived to Arica with the Lake-Louise questionnaire and in children with the modified Children’s Lake-Louise Score for preverbal subjects on arrival at Putre and in next morning. Results: An important desaturation among the children in Putre (84.3% p < 0.001) in comparison with a children that live in Putre (90.3 ± 3 no-Aymaras) and (91.2 ± 2, Aymaras). A major heart rate was observed is children in Putre (124 ± 11 in comparison with children no Aymaras that live in Putre (113 ± 6, p < 0.02) and children Aymaras that live in Putre (101 ± 12, p < 0.0001). A higher incidence of AMS was observed in children (87%) in Putre. Conclusion: Our results corroborate that children are extremely sensitive to hypoxia, as expressed by symptoms of AMS, significant desaturation and major values of heart rate, in no-Aymaras children exposes acutely to high altitude. Our findings add to the available information regarding the problems encountered when ascending to high altitude with children and support the importance of close monitoring of young children during ascent to high altitude. VRA-UDP

HEMATOLOGICAL STUDY IN AYMARAS WITH CHRONIC EXPOSURE TO HIGH ALTITUDE (PUTRE 3500 M).

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Background: Haematological studies makes in Aymaras in La Paz (Bolivia) show values of hemoglobin concentration of 18.8 g/dl. In contrast, with the previously described, Sharps have low level of hemoglobin concentration near 16.6 g/dl. Objective: Determine in Aymaras population at 3500 m (Putre, Chile) hematological parameters. Subjects and Methods: Haematological parameters were measured in 45 voluntaries Aymaras, that live chronically in Putre. Blood sample were take from vein to determined hemoglobin concentration (g/dl); haemacrit (%); Red cell count (mill/mm2); formula was calculated: HCM, CHCM, and VCM (Cell-Dyne 1400). All values are express in mean ± SD. Results: Haemoglobin concentration of 14.9 ± 2.4 g/dl; Haematocrite of 43.9 ± 6.3%; red cell count: 4.85 ± 0.55 mill/mm2; and values of formula of HCM: 30.3 ± 2.4; MCHM: 33.9 ± 1.2 and VCM: 89.4 ± 5.7. Conclusion: Lower values in all haematological parameters were observed in subjects that live in Putre at 3500 m. These evidences could be suggesting a problem in a deficiency of ferrous in the population or that Aymaras population have express a difference with the Aymaras population of Bolivia.

CIRCADIAN RHYTHM OF ERYTHROPOIETIN IN ANDEAN ALTITUDE NATIVES WITH AND WITHOUT EXCESSIVE ERYTHROCYTOSIS.

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Excessive erythrocytosis (EE) is frequent in the Andean region, by effect of chronic maladaptation to high altitude. Despite its poor prognosis, the main determinants are still poorly understood. Erythropoietin (Epo) levels are increased in subjects with EE, but with large individual variation. At sea level and in healthy subjects, a circadian variation of Epo (circ-Epo) has been described, with a nadir in the morning (8:00 AM) and a zenith during late evening (10:00–12:00 PM). The circ-Epo has never been determined in high altitude residents, with or without EE. In 20 Andean male natives of Cerro de Pasco, 4338m, Peru (10 with EE: hematocrit 76.6 ± 1.3%, hemoglobin 23.5 ± 0.3 g/dl, age 38.9 ± 2.5yr, and 10 controls: hematocrit 54.4 ± 0.8%, hemoglobin 16.9 ± 1.0 g/dl, p < 0.001, age 38.5 ± 1.4yr) we tested whether: 1) a circ-Epo were present in controls 2) a specific alteration in circadian rhythmicity were present in subjects with EE that could be related to a possible day or night stimulus. Epo was measured (by Elisa, R&D) from sera obtained every 4 hours, starting 8:00 AM. During night a sample was taken at 5:00 AM instead of 4:00, to leave 5 hours of undisturbed sleep. Control subjects showed normal morning Epo, with a marked circ-Epo, with nadir at 8:00 AM, and zenith at midnight, with a 8:00AM–12PM variation of 65 ± 33%. EE showed consistently higher Epo values during day and night (p < 0.001, ANOVA), with completely disrupted circ-Epo due to a loss of the morning nadir, with no clear zenith. The 8:00AM–12PM variation was z = 2 ± 0.5 (p < 0.05 vs controls subjects). Conclusions: 1) Andean subjects without EE have a normal circadian rhythm of Epo; 2) the circadian rhythm is disrupted in EE due to the contribution of factors acting during both night and day.
Conclusions: The process of acclimatization to the hypoxia of altitude is associated with changes in ventilatory and cerebral blood flow (CBF). However, the role of changes in CBF in ventilatory acclimatization to hypoxia is poorly understood. In acute mountain sickness (AMS) and high altitude cerebral edema (HACE) remaining oxygenation may be relevant in determining both the cerebrovascular and ventilatory responses to incremental isocapnic hypoxia. Moreover, the hypothesis that nocturnal hypoxemia due to sleep-disordered breathing (SDB) may determine excessive erythropoietin (Epo) production. Methods: Two nights standard polysomnography (baseline and after oxygen administration), Serum Epo levels measured in the evening (8:00, 12:00 PM), and next morning (5:00, 8:00, 12:AM). The sleep efficiency and structure, and the number of arousals were similar in the two groups. All subjects showed nocturnal periodic hypopneas. The apnea-hypopnea index (AHI), the duration of the hypopneas and the mean oxyhemoglobin desaturation were similar in both groups (EE: 10 ± 3.4; OV: 1.6 ± 0.8 sec; 6.5 ± 0.6%, respectively; controls: 8.7 ± 2.0 ± 1 sec; 4.6 ± 0.2%, respectively, all NS vs EE). Mean SaO₂ decreased from wakefulness in sleep (EE from 83.7 ± 0.3 to 80. ± 0.1, P < 0.01) and in controls (85.6 ± 0.4 to 82.8 ± 0.5%, P < 0.01) and remained significantly (P < 0.05 or better) lower in EE. Epo levels in the morning correlated with night SaO₂ and EPO production. This short protocol appears well suited to quantify the cerebrovascular and ventilatory responses to incremental isocapnic hypoxia. Moreover, it may help further study the role of changes in CBF in VAH with chronic or intermittent hypoxia, and in the aetiology of diseases such asAMS and HACE. This study approved by Conjoint Ethics Board and supported by AHFMR, HSFA, and CIHR. 1.1. Tansley et al., J. Appl. Physiol. 95(4): 1263–1271, 2002.

Conclusions: We conclude that the NIRS fast resaturation technique a) does not alter cerebral blood flow; b) produces values similar to accepted methods, and thus can be used to measure the time course of CBV changes during field and simulated high altitude experiments.
CEREBRAL DESATURATION AT VO2 MAX AT HIGH ALTITUDE (5250M).

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Ascent to altitude results in peripheral desaturation. Exercise at high altitude compounds this desaturation. This study aimed to assess cerebral desaturation at rest and on exercising to VO2 max at 5250m. Methods: 9 subjects (1 female, age 32–60) were studied at 5250m. Pulse oximetry (SpO2) was measured using a Ohmeda Biox 3740 Pulse Oximeter; Regional cerebral oxygenation (rSO2) was measured using a Critikon 2020 monitor; middle cerebral artery velocity (MCAV) was assessed using a DWL Multi Dop T1. COLIN CBM-7000 continuous beat to beat blood pressure monitor was used to measure blood pressure. A purpose built collapsable recumbent exercise bicycle was constructed by QinetiQ, Farnborough UK. Statistics: Paired t test. Results: Exercise to VO2Max at 5250m resulted in an increase in pulse rate from 72.1(11.8) to 129.9(5.3) (p < 0.0001). No change in mean arterial blood pressure 106.6(10.7) to 110.2(21.9)mmHg (p = 0.501). SpO2 fell from 81.8(4.7)% to 65.7(10.7)% (p < 0.0001). rSO2 fell from 61.8(3.5)% to 58.2(2.5)% (p = 0.0019). MCAV fell from 75.1(19.3)cm/sec to 68(17.2) cm/sec (p = 0.0017).

The EFFECT OF AN OXYGEN BULUS ON CEREBRAL OXYGENATION AND BLOOD FLOW AT ALTITUDE.

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Cerebral hypoxia is central to the pathophysiology of acute mountain sickness (AMS). Whilst the beneficial effects of supplemental oxygen is well recognized, the effect of oxygen on cerebral haemodynamics at altitude is not clearly understood. Introduction: Above 3560 m, voluntary hyperventilation improves arterial oxygen saturation (SaO2) and cerebral regional oxygenation (rSO2) (1). At sea level, hypercapnia improves cerebral blood flow (CBF) and rSO2 even if hypoxic end-tidal PO2 is maintained (2). We tested if an increased CBF due to increased PCO2 and reduced PO2 associated with hyperventilation (HVE) improves rSO2 at altitude. Methods: Five healthy male subjects partially acclimated to 4750 m breathed on a partial rebreathing circuit that limited alveolar ventilation (VA) to the flow of air entering the circuit. Subjects hyperventilated voluntarily while air intake to the circuit was reduced. PETCO2, SaO2, rSO2, and middle cerebral artery blood velocity (MCABV), an index of CBF, were measured. Brain O2 delivery (D02) was calculated as MCABV × SaO2. Results: At rest, PETCO2 was 27.3 ± 1.4 (SD) mmHg, SaO2 90.8 ± 2.7%, rSO2 64.0 ± 2.0%, and MCABV 66.5 ± 10.6 cm/s. Changes from resting values (p < 0.01) are presented below. In three subjects, the initial phase of hyperventilation depleted blood CO2 content such that the reduction in air intake (i.e., VA) caused a disproportionate hypoxia prior to any rise in PETCO2. Results from the remaining two subjects are presented in the table. Discussion: Assumingly constant cerebral O2 extraction, our data imply that, at altitude, rSO2 is more influenced by the blood-tissue O2 gradient than by perfusion. Clin Sci 2000;98:159 J Clin Monit 2000;16:191.

REGION SPECIFIC CHANGES IN CEREBRAL GLUCOSE METABOLISM FOLLOWING HIGH ALTITUDE EXPEDITION.

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Functional and cognitive impairment has been reported in high altitude elite climbers. However, little is known about changes in cerebral glucose metabolism following high altitude expeditions. Five healthy male subjects partially acclimated to 4750 m breathed on a partial rebreathing circuit that limited alveolar ventilation (VA) to the flow of air entering the circuit. Subjects hyperventilated voluntarily while air intake to the circuit was reduced. PETCO2, SaO2, rSO2, and middle cerebral artery blood velocity (MCABV), an index of CBF, were measured. Brain O2 delivery (D02) was calculated as MCABV × SaO2. Results: At rest, PETCO2 was 27.3 ± 1.4 (SD) mmHg, SaO2 90.8 ± 2.7%, rSO2 64.0 ± 2.0%, and MCABV 66.5 ± 10.6 cm/s. Changes from resting values (p < 0.01) are presented below. In three subjects, the initial phase of hyperventilation depleted blood CO2 content such that the reduction in air intake (i.e., VA) caused a disproportionate hypoxia prior to any rise in PETCO2. Results from the remaining two subjects are presented in the table. Discussion: Assumingly constant cerebral O2 extraction, our data imply that, at altitude, rSO2 is more influenced by the blood-tissue O2 gradient than by perfusion. Clin Sci 2000;98:159 J Clin Monit 2000;16:191.
57. SUPINE EXERCISE CYCLE ERGOMETER FOR CEREBRAL STUDIES.
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l NHS Trust, Warrington, UK;3, The Medical School, Univ Birmingham, UK;4, stevoharris@ukgateway.net.

Objective An exercise ergometer was required for cerebral studies under expedition conditions. The Exercise Ergometer The ergometer was designed and developed with several novel features: The subject peddals in a supine position with the head fully supported. This allows position-critical and vibration-sensitive monitoring techniques during exercise, such as Trans-Cranial Doppler for cerebral blood flow. A strain-gauged crankset allows power measurement, independent of atmospheric conditions. An adjustable brake controls resistance. A flywheel promotes smooth pedaling, comparable to cycling on the flat. To minimize weight, appropriate inertia is obtained by gearing a small flywheel to rotate at high speed. It is adjustable for people from 3'4" to 6'2" in height. It can be folded and carried like a rucksack.

Method Nine subjects were tested at four locations in the UK and Bolivia, at altitudes between 92m and 5260m. At each altitude, the resistance was incrementally increased to volitional exhaustion to determine the power at VO2max. Subsequently, graded exercise tests were performed, working for 5 minutes each at a steady state of 30%, 50% and 70% of VO2max power.

Results Concurrent measurements were made of power, cadence, expired gases, cerebral blood flow, cerebral regional oxygenation, blood pressure and pulse rate. The results were correlated and are reported in complementary papers. Conclusion The exercise ergometer worked reliably for the duration of the study, including a 2-week period at high altitude. It proved easy to use, compatible with other test equipment, robust yet lightweight and portable. It has the potential to be a standard tool for high-altitude exercise research and other test or rehabilitation applications where the head or body needs to be supported, such as when monitoring cerebral functions.

58. IMPROVED CEREBRAL OXYGENATION DURING ACUTE HYPERVENTILATION AT ALTITUDE IS NOT DUE TO IMPROVED CEREBRAL BLOOD FLOW.
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An inadequate hyperventilatory response may contribute to the development of acute mountain sickness (AMS) in susceptible individuals. Whilst the effect of hyperventilation on cerebral blood flow and oxygenation at sea level is predictable, the physiological impact of hyperventilation on brain oxygenation at altitude remains poorly understood. Aim: To study the effects of acute hyperventilation on cerebral oxygenation at altitude. Methods: 11 healthy male subjects breathing ambient air at 5260m underwent 60 seconds of maximal hyperventilation following which each subject was allowed to breathe normally for 3 minutes. Data were recorded at baseline and 2 second intervals using the following parameters: peripheral oxygen saturation by earlobe pulse oximetry (SaO2), cerebral oxygen saturation by near infrared spectroscopy (rSO2), middle cerebral artery velocities by transcranial Doppler (MCV), continuous non-invasive blood pressure monitoring (mBP), and pulse rate (PR).

Results: The physiological response during the brief spell of acute hyperventilation were as follows: (* significant) Conclusion: There is a significant rise in cerebral oxygenation with hyperventilation despite a drop in middle cerebral artery velocities and an insignificant change in peripheral oxygen saturation. This suggests that oxygen flux in the brain during high altitude acute hyperventilation might be due to a mechanism unrelated to cerebral blood flow.

59. REACTIVE OXYGEN SPECIES (ROS) PRODUCTION DURING EXPOSURE TO PROGRESSIVE HYPOBARIC HYPOXIA.
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The relationship between hypoxia exposure and ROS generation is quite complex. Several lines of evidence show that ROS are generated during hypoxia but most of this evidence has been obtained in vitro and relevance in humans is not yet well known. Aim to study ROS generation in healthy lowlanders during high altitude exposure. Method 5 lowlanders (3M, 2F) climbed from 1300 to 5030m (Pyramid Lab, Khumbu Valley, Nepal). At altitudes of 1300m, 3500m, 4040m and 5050m samples of nasal fluid lavage were obtained (by instillation of saline solution), filtered and stored in liquid nitrogen. As index of oxidative stress we measured the activity of xantine-oxidase, an hydroxylase that produces superoxide and uric acid from purine substrates and molecular oxygen, by measuring uric acid. The presence of uric acid was evaluated trough "Uricle test", a spectrophotometric measurement made before and after addition of Urato-oxidase enzyme. Results due to technical problems only 3 subjects completed the protocol. Data of each subject are reported in the figure showing an increase of uric acid production with altitude. We conclude that progressive exposure to hypoxia induces an oxidative stress.

The result suggest that hypoxia led to an increase in the production of ROS also in humans.

60. HEMODYNAMIC EFFECTS OF SUPPLEMENTARY OXYGEN DURING EXERCISE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE.
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Exercise endurance in severe COPD is improved with supplementary oxygen (SO), which may be partly related to improvements in cardiac output (CO). 16 patients with severe COPD (FEV1 34 ± 7% of predicted) performed two bicycle exercise tests: one breathing room air (RA) and one breathing SO at a flow rate of 4 l min−1 (FIO2 = 0.35). Testing sequence was randomized and double blinded, with 30 minutes of rest in between tests. Measurements were made of SaO2, minute ventilation (VE), heart rate (HR) and cardiac output (CO) by means of electrical impedance cardiography. With SO, endurance time increased from 94 ± 23 to 263 ± 66 s (P < 0.001). In RA, SaO2 decreased from 94 ± 2% at rest to 86 ± 5% at end-exercise. SaO2 didn’t change during exercise in SO (97 ± 1% at rest; 95 ± 3% at end-exercise). In RA, end-exercise VE was higher than after an equivalent exercise duration in SO (34.7 ± 11.0 vs 29.8 ± 9.2 l/min, P < 0.001). At end-exercise in SO, VE increased to 33.7 ± 10.3 l/min, not different from end-exercise in RA. There were no differences in end-exercise HR (124 ± 13 in RA vs 126 ± 13 beats/min in SO). End-exercise CO increased from 7.7 ± 2.6 in RA to 8.6 ± 2.3 l/min/m2 in SO (P = 0.01). The increase in endurance time was significantly correlated to both the reduction in VE (R = 0.62, P = 0.01; comparing end-exercise RA to an equivalent duration in SO), and the increase in CO (R = 0.69, P = 0.004; comparing end-exercise RA to end-exercise SO). It is concluded that in severe COPD, the improved exercise endurance when breathing SO is not only associated with a reduction in ventilatory need, but also with improvements in hemodynamic performance.
**61.** THE MECHANISM OF SHORTENING OF VOLUNTARY BREATH HOLDING TIME (VBHT) AT HIGH ALTITUDE.
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This study examines the decrease of voluntary breath holding time (VBHT) with respect to increasing altitude. The aim is to correlate this phenomenon with respiratory regulation. **Materials and Methods:** The subjects in this study were 5 Expeditions from Japan to the Asian Giants. They used their own wristwatches to measure VBHT. To normalize all the data from each Expedition, instead of VBHT, VBHT% was used for the comparison between data at sea level and at altitude. Here, VBHT% = 100 × VBHT at altitude/VBHT at sea level. **Results:** The relationship between VBHT% and altitude is revealed by their graphical relationship. Each line is not a single continuous line, but it is interrupted abruptly at a certain altitude (around 2–3,000m, though it differs between expeditions), then shifted rightward. Only 2 expeditions observed VBHT on descent, in which hard recovery from once shortened VBHT was reported. **Discussion:** The reason for the shortening of breath holding time at high altitude may be that the threshold of PaCO₂ to breaking point of breath-hold was lowered by increase of blood pH. And also the reason of abrupt rightward shift of VBHT%–Altitude line may be that respiratory alkalosis induced by hyperventilation was corrected by stepwise discharge of bicarbonate ion through the kidney. The reason for hard recovery of VBHT even after getting down could be explained by fatigue. **Conclusion:** The rightward shift of VBHT% at high altitude may be a high altitude reaction which indicates renal regulation of respiratory alkalosis, which could be the first step to explaining high altitude acclimatization.

**62.** EFFECT OF ALTITUDE AND DEGREE OF EUROPEAN ADMIXTURE ON THE VENTILATORY RESPONSE TO SUSTAINED HYPOXIA IN SEA LEVEL AND HIGH ALTITUDE NATIVES LIVING AT SEA LEVEL.
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High altitude Andean natives have an irreversibly blunted ventilatory response to hypoxia. This blunting represents the expression of their higher hypoxic ventilatory depression (HVD) due mostly to a decreased fast-OFF response to prolonged hypoxia, rather than to a decreased fast-ON ventilatory response to acute hypoxia. However, Andean natives differ in their level of European admixture rate (ADM, %). With this analysis we aim to estimate whether HVD is jointly affected by hypoxia, and different degrees of ADM in sea level and high altitude subjects. We analyze the ventilatory response to sustained (20 min, end-tidal PO₂ = 50 Torr) isocapnic hypoxia in 28 high altitude natives (>3,500 m) residing at sea level (HA, 7.61 ± 6.7 1/min), and on 29 sea level natives (SL, 2.68 ± 8.41/min). HVD values in these two groups were compared to a sea level group (SL-ADM, n = 32) in which ADM had been estimated using a panel of 20 ancestry-informative genetic markers. HVD was 1.41 ± 6.6 1/min in the SL-ADM group (p = N.S. vs SL). Dividing the SL-ADM group into low (c) versus high (c+) ADM subgroups (<1% versus ~18% average European genetic influence, respectively) reveals: HVD SL-ADM(–) = 3.17 ± 7.4 1/min, versus SL-ADM(+) = –0.83 ± 5.11 1/min. Thus, lower ADM is associated with higher HVD values. In addition, HVD correlated inversely with logADM in SL-ADM group (r = 0.36, p < 0.05), yet, the highest HVD values were presented by the HA subjects (p < 0.05 vs SL; p < 0.001 vs SL-ADM (+); p < 0.05 vs SL-ADM (–)). We conclude that both, the place of birth (altitude) and the degree of ADM (more Quecha) might be explaining the differences observed in HVD in the Andean population.

**63.** IMPACT OF BMI ON CPAP IN THE OBSTRUCTIVE SLEEP APNEA SYNDROME.
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**Introduction** In patients with obstructive sleep apnea syndrome (OSAS) a high body mass index (BMI) may be thought to affect inspiratory pressure in CPAP treatment by increasing respiratory load. The aim of this study was to investigate the correlation between BMI and effective CPAP, determined by auto-CPAP titration. **Materials and Methods:** One hundred and one patients with excessive daytime sleepiness had been diagnosed as having OSAS. Before initiation of nocturnal CPAP treatment, the patients were referred to an ambulatory CPAP titration (AutoSet T, ResMed, Australia). The auto-titration data were then compared to the patient’s body mass index by means of correlation analysis. **Results:** The analyses of the 95 percentile and median auto-CPAP pressures and the patients BMI showed a weak, but statistically significant correlation between these parameters. **Discussion and conclusion:** A positive correlation between BMI and effective nocturnal CPAP is in line with clinical experience. However our findings show that the strength in this correlation is so weak that even large variations in BMI do not affect treatment pressure significantly.

**64.** CAPNOGRAPHY AT HIGH ALTITUDE.
Kyle Pattinson¹, Steve Myers², Catherine Gardner-Thorpe³. Birmingham Childrens Hospital, Birmingham, UK.¹ Centre for Human Sciences, Qinetiq, Farnborough, UK.² Stoke Mandeville Hospital, Aylesbury, Buckinghamshire, UK.³ kyle999@pobox.com.

**OBJECTIVES** The purpose of the experiment was to elucidate factors associated with capnograph malfunction, a common problem on altitude research expeditions. **METHODS** Four capnographs were tested in altitude chambers at all altitudes corresponding with those during our recent experiments in Bolivia (see table below). The following parameters were measured Flow rates through each capnographs tubing using a rotameter A gas containing 5% CO₂ was used to measure calibration. Machines were not recalibrated before altitudes. **RESULTS** (X = No reading) **CONCLUSIONS** Altitude affects capnograph function independently of other environmental variables. These results correspond with field observations. Flow rates in all monitors other than K4b2 decrease with decreasing barometric pressure until the machine no longer reads. Following this, flow rate is unpredictable. Collective fan laws predict reduced flow with decreased barometric pressure.1 Changes in CO₂ readings emphasize the importance of recalibration on change of altitude. An altered refractive index of air is the likely explanation.2 K2b4 appears to compensate. Electromics in some monitors may sense reduced barometric pressure and air leak within the monitor. K4b2 is the only monitor that tested which is functional at 18000 feet. **REFERENCES** CHEST 1995;108:1817–80 Personal communication. Datex-Omheda, Finland.

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**1** Fabiola León-Velarde, María Rivera-Chira, Alfredo Gamboa. fabiote@upch.edu.pe.
65. HYPOBARIC HYPOXIA IS NOT A DYSPNOGENIC FACTOR IN HEALTHY SUBJECTS AT REST.
Ichiro Kuwahira1, Tokuzen Iwamoto, Makoto Ishii2, Kazutaka Kamio, Mai Nishiumi3, Kenji Eguchi4, Tokai Univ Tokyo Hospital5, Tokai Univ School of Medicine6. kuwahira@tok.u-tokai.ac.jp.

Dyspnea is a complex symptom. Sensations of difficult breathing in cardiorespiratory diseases may vary in quality and may have different pathophysiological bases. Lack of oxygen may exert its effects on dyspnea via both an increase in ventilation and as a direct dyspneic stimulus. However, relatively few studies have formally examined the effects of hypoxia on dyspnea, and the relationship between hypoxia and dyspnea is unclear. In the present study, we evaluated changes in arterial blood gases, the magnitude of dyspnea (Borg scale) and the level of consciousness (mini-mental state examination, MMSE) in 27 healthy male subjects, using a hypobaric hypoxic chamber in which the barometric pressure was gradually lowered to a simulated altitude of 6000 m, at a rate of 30 m/min (2 Torr/min). The subjects included both mountain climbers and non-climbers. Arterial blood samples were obtained at an interval of 1000 m via a catheter inserted into the radial artery. All measurements were carried out during the resting state at a sitting position. Two medical doctors breathing oxygen entered the chamber for the measurements and for safety of the subjects. The mean PaO2 at a simulated altitude of 0, 2000, 3000, 4000 and 6000 m were 95.4 ± 4.1 (SD), 68.1 ± 6.5, 55.3 ± 5.3, 46.8 ± 4.8, 41.8 ± 4.9 Torr, and the PaCO2 were 40.0 ± 1.9, 38.9 ± 2.9, 38.4 ± 2.1, 36.8 ± 3.0 and 31.9 ± 2.3 Torr. While there was a significant decrease in PaO2 and PaCO2, the Borg scale and the score of MMSE did not change even at the simulated altitude of 6000 m. No subjects complained of dyspnea during the study. These results indicate that hypobaric hypoxia is not a dyspneic factor in healthy subjects at rest and that an increase in ventilation derived from heightened ventilatory demand does not produce dyspnea at rest (Grant-in-Aid for Scientific Research Japan #12670578).

66. EFFECTS OF CHRONIC HYPOBARIC HYPOXIA ON UPPER AIRWAY EMG RESPONSES TO ACUTE HYPOXIA AND ASPHYXIA IN THE RAT.
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The upper airway (UA) dilator muscles play a crucial role in maintaining airway patency. We recently demonstrated that chronic intermittent hypoxic hypoxia impairs rat UA EMG responses to acute hypoxia and asphyxia. This finding may be particularly relevant to clinical disorders that are characterized by recurrent episodic hypoxia such as the sleep apnoea syndrome. Chronic exposure to prolonged continuous hypoxia occurs in healthy humans in various circumstances, however very little is known about the effects of chronic hypoxia on UA muscle function. The present study was designed to examine the effects of long-term exposure to continuous hypoxia on UA EMG activity and responses to acute physiological stimuli. Adult male rats were exposed to normoxia (n = 5) or hypobaric hypoxia (n = 5, barometric pressure 450 mmHg) for 6 weeks. At the end of this period, sternohyoid (a representative UA dilator muscle) EMG activity was recorded during normoxia, hypoxia (10% O2 in N2) and asphyxia (2% O2 and 3% CO2 under pentobarbitone anaesthesia). Chronic hypobaric hypoxia significantly reduced sternohyoid EMG responses to acute hypoxia (+23.1% vs +3.1%, % change from baseline, normoxia vs. hypoxia) and asphyxia (+32.0% vs +6.7%). In summary, chronic continuous hypobaric hypoxia significantly impairs (blunts) rat UA EMG responses to acute hypoxia and asphyxia. Impairing reflex activation of the UA dilator muscles predisposes to UA collapse, which could lead to further hypoxemia thereby exacerbating the condition. The results may also partly explain the association of obstructive sleep apnoea and chronic obstructive pulmonary disease, the so-called “overlap syndrome.” Supported by Univ College Dublin, Ireland and the Royal College of Surgeons in Ireland.

67. EFFECT OF L-ARGININE SUPPLEMENTATION ON EXPIRED NO AND RESPIRATORY SYMPTOMOLOGY WITH ACUTE EXPOSURE TO AN ALTITUDE OF 4383 METERS.
Takafumi Azami1, David Preiss2, Len Goodman3, Ron Somogyi4, Eitan Prisman5, Alex Vesely6, Steve Isscoe7, Kyle Patterson8, Jo Bradwell9. Nagoya City Univ Hospital1, Univ Toronto, York Univ2, Queens Univ3, Birmingham Medical Research Expeditionary Society4. tazami509@t.aid.com.

Introduction: Hyperventilation at altitude increases SaO2 and PAO2, but decreases PACO2. The combination of reduced cerebral blood flow and increased affinity of Hb for O2 due to the respiratory alkalosis would reduce cerebral O2 delivery. We devised breathing circuits to maintain PACO2 constant during hyperoxia (iso-CO2 and PAO2) and PAO2 constant during hyperventilation (iso-O2). Our aim was to identify the contribution of hypocapnia to the hyperventilation-associated increase in SaO2 at altitude. Methods: Five healthy males were studied at 4750 m. Each was studied while breathing through a sham circuit, the iso-O2 circuit, hyperventilation decreased PACO2 by 11.4 ± 2.7 mmHg, NS). In all three conditions, the increase in SaO2 was a function of the slope of the Hb-O2 delivery circuits at resting ventilation, and after 5 min of breathing at 4× resting ventilation. We monitored SaO2 and tidal PO2 and PCO2. Results: With the iso-CO2 circuit, hyperoxia increased PaO2 by 20.5 ± 5.0 mmHg (p < 0.05). With the iso-O2 circuit, hyperventilation decreased PACO2 by 11.4 ± 4.3 mmHg but PaCO2 did not change (14.2 ± 2.7 mmHg, NS). In all three conditions, the increase in SaO2 was a function of the slope of the Hb-O2 dissociation curve at the initial SaO2. Figure 1 illustrates the independent effects of changes in PaO2 and PACO2 on SaO2 during hyperventilation in the subject with the lowest initial SaO2. Discussion: This is the first demonstration of the specific contribution of hypocapnia to increases in SaO2 during hyperventilation at altitude. Decreases in PCO2 contributed little to raising PaO2 but increased the affinity of Hb for O2. The increase in PaO2 accounted for most of the increase in SaO2. The SaO2 data fit, within experimental error, the theoretical predictions of Kellman’s “virtual PO2” equation. Breathing circuits that allow hyperoxia but maintain hypocapnia at altitude may optimize O2 delivery to the brain and other tissues.
WHAT HAPPENS TO RESPIRATORY CHEMOREFLEXES AT ALTITUDE?
Ron Somogyi1, Joseph Fisher2, David Preiss1, Alex Vesely1, Etan Peisman1, AB Bradwell1, Takafumi Azami2, Saaraa Mahamed3, James Duffin4, Univ Toronto, Dept Physiology5, Toronto General Hospital, Dept Anaesthesiology6, Birmingham Medical Research Expeditionary Society7, Univ Toronto, Depts Physiology and Anaesthesiology8. ron.somogyi@utoronto.ca.

Introduction: Ventilatory acclimatization to 3 weeks of altitude hypoxia may result from changes in respiratory chemoreflexes. We measured the thresholds and sensitivities of the central and peripheral respiratory chemoreflexes during chronic exposure to hypoxia at altitude (>3600 m) and after return to sea level, hypothesizing that they would adapt. Methods: We used modified rebreathing tests at end-tidal isoxic levels of 50 and 150 mmHg to measure the chemoreflexes; the former enhances the peripheral chemoreflex response, and the latter attenuates it so as to measure the central chemoreflex response. Five healthy male volunteers performed the two rebreathing tests at sea level, 2 days (acute) and 17 days (chronic) after arrival at 3600 m, and 2 and 5 days after returning to sea level. [HCO3-] and [H+] of venous blood samples were measured at sea level, after 17 days at altitude, and during de-acclimatization. Results: The chemoreflex sensitivity to CO2 at both levels of isoxia was unchanged throughout the test period. However, the chemoreflex CO2 thresholds measured at both isoxic levels decreased significantly (p < 0.05) at altitude and remained decreased until 5 days after returning to sea level, when it increased significantly but remained lower than the pre-exposure control. Nevertheless, when [HCO3–] was used to convert the [H+] thresholds, the threshold changes were no longer evident. By contrast, estimates of steepest isoxic CO2 difference decreased significantly at altitude. Implications: Acclimatization to altitude resulted in increased ventilation as indicated by the decrease in [HCO3–]. Although we hypothesized that changes in the respiratory chemoreflexes would be responsible, none were evident. Consequently, we suggest that changes in strong ion difference may account for the increased ventilation.

PHYSIOLOGICAL EFFECT OF COORDINATED BREATHING UNDER HYPOXIC ENVIRONMENT: A QUANTITATIVE STUDY OF DEEP AND ABDOMINAL BREATHING.
Shunsuke Kokubu1, Taketeru Maekawa1, Masayoshi Yamamoto1. National Institute Fitness Sports in Kanoya1. m0160101@sky.nifs.k.ac.jp.

Voluntary coordinated breathing such as hyperventilation is effective method to avoid decreasing SpO2 under a hypoxic environment. However, we also suffer negative effects such as extra loss of CO2 body fluid and temperature because of the remarkable increase of ventilation volume. To find reasonable breathing method under a hypoxic environment. Therefore, the AB is more reasonable breathing method under a hypoxic environment.

CHANGES IN HYPOXIC VENTILATORY RESPONSE (HVR) DURING 8 WEEKS AT 3800M ALTITUDE.

Ventilatory acclimatization to hypoxia increases ventilation (VI) and the isocapnic HVR over 2 to 14 days of hypoxia but previous results suggest that HVR may decrease again after 4 weeks at altitude (Wild. Env. Med 11: 172–179, 2000). We measured the course of acclimatization in humans (4 M, 1 F: 23–41 yrs) at sea level and during 8 weeks at 3800m (PIO2 ~ 90 Torr). HVR (ΔVI/ΔSaO2) was measured after pre-oxygenation (PIO2 > 200 Torr 20 min) by stepping to SaO2 = 90% maintaining PETCO2 = 2.5 Torr above the hyperventilatory value. Isocapnic HVR was measured again by stepping to SaO2 = 80% after 5 and 11 min at SaO2 = 90% to quantify hypoxic ventilatory decline (HVD). Subjects increased PaO2 and SaO2 breathing ambient air during 8 wks at altitude. HVR increased after 1 day and remained elevated after 8 wks (p < 0.05). HVR decreased after 8 min of acute hypoxia and VI decreased further after 14 min of acute hypoxia without further change in HVR (p < 0.05). Hence, HVD manifest as an initial decrease in O2-sensitivity but later as a general decrease in ventilatory drive. This pattern of HVD was similar at all time points. Hence, hypoxic desensitization and blunting of the HVR did not occur after 8 wks of hypoxia in these subjects and changes in the HVR during 8 wks of hypoxia do not involve changes in HVD. Support: NIHMOI RRO8827, NIHHL17731, and WMR5.
ADAPTATION OF VENTILATION IN MOUNTAINEERS CLIMBING TO 4599M.

Konrad E Bloch1, Oliver Senn1, Manuel Fischer2, Rahul Thalmann2, Marco Maggiorini2, Pulmonary Division, Univ Hosp, Zurich, Switzerland1, Medical Intensive Care, Univ Hospital, Zurich, Switzerland2

We investigated ventilatory adaptation in unrestrained mountaineers climbing in the high Alps. 26 volunteers were studied in Zurich (490m) before ascending to Mt. Rosa and while climbing from 3650m to 4599m within 4-6 hours with a break at 4200m. Breathing patterns were continuously monitored without airway instrumentation using novel, light-weight equipment incorporating calibrated respiratory inductance plethysmography, pulse oximetry and ECG. In each subject breathing pattern variables, oxygen saturation (SpO2) and heart rate were averaged over 10 minutes at various altitudes at rest, and during hiking. Rebreathing into a bag of known volume at various altitudes confirmed accuracy of tidal volumes by respiratory inductance plethysmography within 15%. The table shows group means (+SE). After 1 night at 4599m ventilation at rest remained unchanged at 8.8 ± 0.6 L/min, SpO2 increased to 81 ± 0.8%

Thursday February 22nd 2003

DNA MICROARRAY ANALYSIS OF HYPOXIA-INDUCED FATIGUE IN SKELETAL MUSCLE.

Dale McCall1, Dargan Frierson1, James Blum1, Martyn Knowles1, Stephen Kriwosez1, U. Northern Carolina-Wilmington, 1

We are presenting results of extension to cDNA microarray analysis of tests of a genetic model of hypoxia-induced fatigue in skeletal muscle. Mathematical modeling and subsequent confirmatory breeding tests showed that, in mice, heritable differences in tolerance of treadmill exercise (time elapsed to a behavioral endpoint, etc.) in HgO-Po2 150% to 50% for 8 weeks' exposure to 380 Torr is associated predominantly with the expression of 2 unlinked autosomal loci. A striking feature of the inheritance pattern is the presence in the hypoxia-exposed F1, but not in the normoxic control F1 sample, of a very large epistatic interaction between the two loci. However, the magnitude of the genetic effect and its variability decreased somewhat in successive generations formed from backcrosses to the low-performing parental strain, which is indicative of lesser contributions from modifying genes. In order more completely to characterize genetic contribution to the test variable, tet DNA microarray (Invitrogen Corp.) experiments were performed to measure levels of expression in 5184 genes in the non-segregating generation 3. Inbred strains (C57BL/6 and BALB/c) were F1-hybridized and in normaloxia/hypoxia comparisons for each genotype (N = 5 for each of 6 experimental cells). Data were transformed and standardized to a uniform scale across all 32 arrays. Analysis was done using Significance Analysis of Microarrays (SAM) software (Tusher, et al., 2001, PNAS 98(9): 5116-5121) with minimal false discovery rate (FDR) correction. Significant differences in gene expression were uncovered in each comparison. Included as candidate genes are Hypoxia-inducible factor 1 alpha, Coflin 2 (muscle isoform), Heat shock protein 71kDa, Beta-actin, and two protein kinases. Although the analysis is in an early stage, the number of genes involved is small. This raises the possibility of critically defining both the inheritance of differences in fatigue in skeletal muscle induced by a particular type of exercise and the associated physiology.

EFFECT OF PROGRESSIVE HYPOXIA WITH MODERATE HYPERCAPNIA ON VENTILATORY VS. VAS RESPONSES IN HUMANS.

Atsuko Masuda1, Yoshiakazu Sakakibara2, Yoshio Ohyabu3, Chikako Yoshino4, Toshio Kobayashi5, Teisue Komatsu3, Michiko Tanaka5, Shigeru Masuyama6, Yoshiyuki Honda7, Tokyo Medical and Dental Univ1, Kanazawa Institute Univ2, Kogakuin Univ3, Chiba College of Allied Medical Sciences4, Yamamoto Prefectural Univ5, Miyazaki Prefectural Nursing Univ6, Chiba Univ7, gyg02153@sinfy.ne.jp.

Objective: Ventilatory response to CO2 combined with hypoxic stimulation has been well documented as exhibiting a positive interaction between the two stimuli. Using modified Read's method, we previously confirmed this in an open loop CO2-ventilation condition (Respir. Physiol. 126, 17-181, 2001). The purpose of this study is to compare the effect of progressive hypoxia with moderate hypercapnia on ventilatory and respiratory sensation responses in humans. Methods: This study was carried out on 15 young healthy adults (4 males and 11 females). The subjects were exposed to progressive hypoxia under three different end-tidal PCO2 (PETCO2) levels: normocapnia, 2, and 4 mmHg higher than normocapnia. Defined as NC0, HC2 and HC4 runs, respectively. We measured ventilatory parameters and respiratory sensation by visual analog scale (VAS). Results: The slope of the SpO2-ventilation response curve became steeper as the PETCO2 elevated. There was significant slope augmentation in the HC4 run compared with the NC0 run (p < 0.05 vs. -0.40 l/min/%SpO2, p < 0.05). On the other hand, the slope of the SpO2-VAS response curve exhibited no significant change. Conclusion: Our study showed that moderate steady hypoxia synergistically augmented the ventilatory response to progressive hypoxia whereas such positive interaction was not detected in the VAS response. We speculate that the metabolic ventilatory and behavioral respiratory control systems may have played a more of a role in the former and latter findings, respectively.

HYPOTHERMIA ADAPTATION IMPROVES HEART-TOLERANCE TO HYPOXIA: STUDY ON FUNCTION AND MITOCHONDRIAL GENE EXPRESSION.

Xue-Han Ning1, Shi-Han Chen1, Cheng-Su Xu2, Linheng Li3, Ouiti Hyyri2, Kun Qian3, Julia Krueger2, Micheal Portman1, 1Univ. of Washington/Childrens Hospital & Med Ctr, 1Univ of Washington, xh@u.washington.edu.

Previously we have used cross adaptation to test adaptive capacity in mountaineering performance. We also observed that hypothermia treatment prior to ischemia could induce cross adaptation to resist subsequent ischemia with accumulation of metabolites in both hearts (Ning et al. AJP 274-H1786, 1999; JAF 92-2000, 2002). In this study we proved further evidence for hypothermia protection during myocardial hypoxia without metabolism accumulation. Two Langendorff rabbit heart groups were subjected to hypoxia (Infusate PO2 = 38 mmHg). A hypothermia group (H) was progressively reduced temperature to 29°C within 20 min and maintained for 10 min prior to hypoxia, and for 45 min during hypoxia. The re-oxxygenation was completed at 37°C for 45 min. A normothermia control group (C) was held constantly at 37°C. Pilot study showed that this protocol was the best one to improve tolerance, although treatment with 29°C either prior to or during hypoxia also showed protection. Lactate and CO2 levels were measured in the coronary effluent to monitor metabolite status. Hypothermia prior to hypoxia decreased myocardial oxygen consumption (MVO2) 79 ± 3% of the baseline value and significantly increased oxygen efficiency estimated by dP/dt max/MVO2 and PRP/MVO2, where PRP is developed pressure (DP) × heart rate. Hypothermia improved functional recovery about 3-fold (P < 0.05 vs. C) during re-oxxygenation, including DP, dP/dt max, PRP, and MVO2. Hypothermia hearts maintained mRNA level for mitochondrial membrane specific protein F1-ATPase, while it decreased in C. However, hypothermia did not further enhance F1-ATPase signaling, indicating cross adaptation directly in the organ.
77. NON-INVASIVE BEAT-TO-BEAT BLOOD PRESSURE MEASUREMENT AT HIGH ALTITUDE.
Phil Collins1, Tim Harvey1, Maggie Beazely1, Peter Hillenbrand1, Chris Imray1. BMRES1, chrisimray@aol.com.

Introduction Non-invasive beat-to-beat blood pressure measurements were undertaken during various physiological tests performed by the Birmingham Medical Research Expedition Society (BMRES) at high altitude. The blood pressure measurements were taken to complement cerebral blood flow velocity, cerebral and peripheral perfusion and respiratory gas measurements during exercise, hyperventilation, oxygen bolus and Viagra studies. Method Beat-to-beat blood pressure was measured by the validated radial artery tonometry technique utilizing a Colin Medical CBM-7000 continuous blood pressure monitor (Aichi, 485-8502, Japan). The principle of applanation tonometry involves the artery being partially compressed, against a hard surface, in this case the radial bone. The Colin arterial tonometry method uses a linear array of piezoelectric transducers located in a wrist sensor housing. The sensor exerts sufficient pressure on the skin to partially flatten the underlying artery; the intra-arterial pressure is then transmitted to the sensor, as the tension forces in the artery wall are perpendicular to the forces exerted by the sensor and by the blood pressure acting on the inner surface of the arterial wall. The resultant arterial waveform is then automatically calibrated with a conventional brachial oscillographic cuff measurement. The Colin CBM-7000 monitor displays numerical beat-to-beat blood pressure values, pulse rate and the arterial blood pressure waveform, which was exported in an analogue format for external recording.

Phil Collins

INTRODUCTION

OPERATION OF A PORTABLE METABOLIC MONITOR AT LOW AMBIENT TEMPERATURE.
Steve Myers1, 2, Steve Itse7, 3, QinetiQ Centre for Human Sciences1, 2. steve.myers7@ntlworld.com.

INTRODUCTION

The Cosmed K4b2 is a lightweight, portable metabolic monitor that measures or calculates over 100 variables. During a recent scientific expedition in Bolivia (5480m) problems were experienced when using the unit at ambient temperatures (Ta) of about 0°C. A study was therefore conducted in an environmental chamber to measure the effect on the unit of low Ta. METHODS At Ta of 22°C and −3°C, ambient air (20.93% O2, 0.04% CO2, balance N2) and a certified calibration gas (16% O2, 5% CO2, balance N2) were sampled continuously for 5 minutes. The O2 and CO2 concentrations, Ta, internal temperature of the unit (Tint), all measured by the unit, were recorded every minute. The unit was tested when powered by mains and battery. The O2 and CO2 sensors were calibrated at Tint of 37°C before each of the 8 tests. RESULTS The results obtained when the unit was battery powered (tabulated below) were similar to those obtained when it was mains powered. CONCLUSION When Ta was −3°C, Tint fell below the 34–37°C range recommended by the manufacturer, which resulted in erroneous O2 and CO2 concentrations. When a small charcoal heater was used to maintain Tint, O2 and CO2 concentrations were recorded correctly. Care should therefore be taken when using the unit low ambient temperatures.

78. CARBOHYDRATE SUPPLEMENTATION AFTER EXERCISE AFFECTS MOOD STATE AT HIGH ALTITUDE.

At sea level, carbohydrate ingestion during prolonged strenuous exercise maintains blood glucose levels, improves performance and, enhances mood. The effect of carbohydrate supplementation on mood after prolonged exercise at high altitude has not been investigated.

PURPOSE: To determine if carbohydrate supplementation during passive recovery from prolonged exhaustive exercise at 4300 m will alter mood state.

METHODS: 16 healthy informed male subjects were divided into 2 groups matched for age (25.2 ± 1.8 yr), weight (77.5 ± 2.9 kg), and VO2max (51.0 ± 2.36 mL/kg/min−1). In double-blind fashion, fasted subjects performed a maximum effort 720 KJ time trial on days 3 and 10 of residence at 4300 m. At the beginning of the time-trial and every 15 minutes thereafter, one group (FED) consumed a 10% carbohydrate solution (0.7 g/kg bw) while the other group (TREATMENT) consumed an indistinguishable placebo drink. Water was given ad lib during exercise. Work rate was self-adjusted. Prior to exercise and during recovery at 5 and 20 min post exercise, subjects completed the Feelings Profile (FP), a 19 item short form (Jackson, et al. 1991) of the Profile of Mood States. Within 20 min post exercise, TREATMENT subjects consumed a 10% carbohydrate (0.7 g/kg bw) drink while the FED group consumed the placebo. Fluid volumes were adjusted for exercise duration.

RESULTS: The results obtained when the unit was at ambient temperature of 20°C were similar to those obtained when it was at ambient temperature of 0°C. The effect on the unit of low Ta was not investigated.

CONCLUSION: During exercise at high altitude, post-exercise carbohydrate supplementation effectively reduces confusion but unexpectedly increases feelings of fatigue. These data may reflect a competition for blood flow between the brain and the carbohydrate-suffused gut. Supported by: The Borgenicht Program, The Jeffress Memorial Trust, The Veterans Administration, and The U.S. Department of Defense.

79. A MUCH SIMPLIFIED METHOD FOR PRECISE AND ACCURATE MEASUREMENT OF VCO2.
David Preiss1, Takafulmi Azami2, Steve Iscoe3, Ron Somogyi1, Eitan Peisman1, Alex Vesely1, David Preiss@utoronto.ca.

Commercial metabolic carts typically measure VCO2 by synchronizing and integrating flow and PCO2 signals—a method prone to error, especially in the presence of some rebreathing. We describe a simplified method of calculating VCO2 using a rebreathing circuit and compare VCO2 so measured with that measured by a metabolic cart and bag collection in 14 volunteers. METHODS: We used a partial rebreathing circuit that presents the fresh gas and then the rebreathed gas in sequence. Turning down the fresh gas flow (FGF) below minute ventilation (VE) results in rebreathed gas entering the anatomic dead space and thus does not affect the PetCO2. VA is identified as the FGF where PetCO2 begins to rise. In that case, VCO2 = FGF × FETCO2. RESULTS: Each bag collection was treated as an independent measurement. The difference (M ± SD) in VCO2 measured by the bag collection and our method was 8 ± 38 mL/min and the metabolic cart was 8 ± 52 mL/min. On a breath-by-breath basis, the coefficient of variation with our technique and the metabolic cart were 3.4% vs. 33.1%, respectively. CONCLUSIONS: VCO2 can be precisely and accurately measured using a partial rebreathing circuit from the fresh gas flow and PetCO2.
**81. EFFECTS OF HYPOXIA AND DEXAMETHASONE ON Na-TRANSPORT OF ALVEOLAR EPITHELIAL CELLS.** Sabine Höschle1, Peter Bärtisch3, Heimo Mairbaur1. Dept. Sports Medicine, Univ. Heidelberg1, 2, heimo.mairbaeur@med.uni-heidelberg.de.

Hypoxia inhibition of alveolar ion transport has been associated with susceptibility to high altitude pulmonary edema. Inhibition of Na-transport activity of alveolar epithelial cells is parallelled by a decrease in the amount of transport-proteins in the plasma membrane. We wanted to know, whether decreased transport-activity is caused by a decrease in expression and weather typical oxygen sensing mechanisms are involved in O2 signaling. Control and dexamethasone-treated (DEX, 1µM) A549 cells were exposed to hypoxia (1.5% O2) and Cobalt-Chloride (100µM) for 24h. Levels of a1-Na/K-pump mRNA measured by PCR increased 4-7-fold by DEX, but were not affected by hypoxia. β1-Na/K-pump mRNA was not increased by DEX, but increased 4.5-fold by hypoxia. DEX abolished the effect of hypoxia on β1-Na/K-pump protein measured by Western blot of whole cell protein was increased by DEX (180%). Hypoxia increased a1-Na/K-pump protein up to 1.5-fold. This is in contrast to earlier findings on Na/K-pump from isolated and plasma membranes. Hypoxia had no effect on DEX treated cells. DEX stimulated the activity of the Na/K-pump measured as ouabain sensitive 86Rb-uptake (+40%). Hypoxia inhibits the Na/K-pump activity in the presence and absence of DEX (−50%). Cobalt had similar effects on expression and activity of the Na/K-pump. mRNA was decreased in hypoxia and by cobalt. GAPD mRNA was increased by hypoxia and cobalt in control and DEX treated cells although levels were lower in DEX. These results indicate that the decrease in alveolar cell ion transport activity upon exposure to hypoxia is not associated with decreased mRNA and Na/K-pump protein expression. Pretreatment of cells with DEX prevents hypoxia effects on expression and increases transport activity in normoxia and hypoxia. Glucocorticoid treatment might therefore be beneficial when alveolar fluid balance is disturbed in HAPE.

**82. ASSOCIATION OF RENIN-ANGIOTENSIN SYSTEM GENES WITH HIGH-ALTITUDE PULMONARY EDEMA.** Hotta Junichi1, Masayuki Hanaoka1, Droma Yunden3, Yoshihiko Katsumaya2, Masao Ota1, Toshiro Kobayashi1, Keishi Kubo1. First Dept Medicine, Shinshu Univ School of Medicine1, Dept Pharmacy, Shinshu Univ School of Health Sci, Dept Legal Medicine, Shinshu Univ School of Medicine1, ydzmyp@hotmail.com.

The crucial pathogenesis of high-altitude pulmonary edema (HAPE) is involved with exaggerated pulmonary hypertension. The renin-angiotensin system (RAS) contributes importantly to the pulmonary hypertension mechanisms involved. Investigating the regulation of vascular tone and the maintenance of electrolytes and volume homeostasis. To elucidate the genetic pathogenesis of RAS under the pathogenesis of HAPE, we undertook the current study to identify insertion/deletion (I/D) polymorphism in the angiotensin converting enzyme (ACE) gene by polymerase chain reaction (PCR), as well as five polymorphisms in the angiotensin II type 1 receptor (AT1R) gene and Met235Thr polymorphism [a substitution of methionine (Met) by threonin (Thr) at the 235th codon] in the angiotensinogen (AGT) gene by PCR following restriction fragment length polymorphism in a Japanese population with 44 HAPE-susceptible subjects (HAPE-s group) and 51 HAPE-resistant mountaineering climbers (HAPE-r group). The results are shown as in the following table. *P value was calculated by X2 test 2×2 contingency table. P < 0.05 was considered statistical difference. It is suggested that a genetic background of the RAS might underlie the pulmonary hypertension in HAPE. The I/D polymorphism of the ACE gene and the G1517T polymorphism of the AT1R gene could be used as genetic markers for predicting the susceptibility to HAPE.

**83. ASSOCIATION OF RENIN-ANGIOTENSIN SYSTEM GENES WITH HIGH-ALTITUDE PULMONARY EDEMA.** Hotta Junichi1, Masayuki Hanaoka1, Droma Yunden3, Yoshihiko Katsumaya2, Masao Ota1, Toshiro Kobayashi1, Keishi Kubo1. First Dept Medicine, Shinshu Univ School of Medicine1, Dept Pharmacy, Shinshu Univ School of Health Sci, Dept Legal Medicine, Shinshu Univ School of Medicine1, ydzmyp@hotmail.com.

A blunted hypoxic ventilatory response (HVR) is proposed as a potential mechanism in the pathogenesis of high-altitude pulmonary edema (HAPE). Tyrosine hydroxylase (TH) is a rate-limiting enzyme in the carotid body responding to hypoxia to synthesize dopamine neurotransmitter to heighten ventilation. To clarify the genetic background of the TH gene underlying the blunted HVR in HAPE, we examined the informative tetranucleotide (TCTA)n microsatellite repeats of the TH gene by polymerase chain reaction (PCR) following direct sequencing and the Met1Val variant [a variant swapping valine (Val) for methionine (Met) at the codon 81str]. This value did not change during hypoxia indicating an equivalent decrease in total and Na/K-ATPase associated J02. Inhibitors of Na-channels had no significant effect on cellular J02 whereas inhibition of Na/Ca-exchange tended to decrease cellular J02. These results indicate that A549 cells conserve energy upon exposure to hypoxia. Decreasing the activity of the Na/K-ATPase and of Ca-transport contributes to energy saving in hypoxia. J02 is not fully restored by oxygenation after prolonged hypoxia, which indicates adjustments on the level of gene expression.

**84. THE POLYMORPHISMS OF THE TYROSINE HYDROXYLASE GENE IN SUBJECTS SUSCEPTIBLE TO HIGH-ALTITUDE PULMONARY EDEMA.** Hotta Junichi1, Masayuki Hanaoka1, Droma Yunden3, Yoshihiko Katsumaya2, Masao Ota1, Toshiro Kobayashi1, Keishi Kubo1. First Dept Medicine, Shinshu Univ School of Medicine1, Dept Pharmacy, Shinshu Univ School of Health Sci, Dept Legal Medicine, Shinshu Univ School of Medicine1, ydzmyp@hotmail.com.

**85. HYPOXIA REDUCES CELLULAR OXYGEN CONSUMPTION AND Na/K-ATPASE ACTIVITY OF ALVEOLAR EPITHELIAL CELLS.** Kristin Heerlein1, Andreas Schulze2, Peter Bärtisch1, Heimo Mairbaur1, Peter Bärtisch1, Dept. Sports Medicine, Univ. Heidelberg1, Childrens Hospital, Univ. Heidelberg2, kristin_heerlein@med.uni-heidelberg.de.

Hypoxia has been shown to inhibit alveolar Na-reabsorption by decreasing activity and copy number of transporters. The present study was designed to examine the significance of inhibition of ion transporters such as the Na/K-ATPase for the saving of energy during oxygen deprivation. Alveolar epithelial cells (A549 cells) were cultured in normoxia and hypoxia (5% O2, 24h, 20%) in the presence or absence of DEX (50%). Hypoxia in- hibits the Na/K-pump activity in the presence and absence of DEX (−50%). Cobalt had similar effects on expression and activity of the Na/K-pump. mRNA was decreased in hypoxia and by cobalt. GAPD mRNA was increased by hypoxia and cobalt in control and DEX treated cells although levels were lower in DEX. These results indicate that the decrease in alveolar cell ion transport activity upon exposure to hypoxia is not associated with decreased mRNA and Na/K-pump protein expression. Pretreatment of cells with DEX prevents hypoxia effects on expression and increases transport activity in normoxia and hypoxia. Glucocorticoid treatment might therefore be beneficial when alveolar fluid balance is disturbed in HAPE.

**86. HYPOXIA REDUCES CELLULAR OXYGEN CONSUMPTION AND Na/K-ATPASE ACTIVITY OF ALVEOLAR EPITHELIAL CELLS.** Kristin Heerlein1, Andreas Schulze2, Peter Bärtisch1, Heimo Mairbaur1, Peter Bärtisch1, Dept. Sports Medicine, Univ. Heidelberg1, Childrens Hospital, Univ. Heidelberg2, kristin_heerlein@med.uni-heidelberg.de.

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TREATMENT OF HAPE AND HACE WITH NOVEL BREATHING SYSTEM: CASE REPORT.

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Case report: A 65 year old doctor developed confusion, ataxia and myoclonus on the evening of the 39th day of an extramural ascent of 4800m in Bolivia. He had marked periodic breathing, raised JVP, basal crepitations but no papilloedema. SaO2 measured 62%. He improved during 1 hour in a portable hyperbaric chamber (Barrett bag), which simulated a descent to 2700m. However he relapsed within one hour. Methods: Available O2 supply was limited to a full E-sized cylinder containing ~500 L of O2 at 1 A. We applied a new investigational breathing system that combines a fixed O2 flow with entrained ambient air at a definable flow of both. When minute ventilation exceeds the sum of both fresh gas flows (FGF), the balance of the inspirate consists of rebreathed gas. Both FiO2 and VA are determined by the FGF. The patient breathed through the circuit via a modified nasal CPAP mask.

THE EFFECT OF SILDEFANIL (VIAGRA) ON CEREBRAL HAEMODYNAMICS AT ALTITUDE.

Colin Chan1, Phil Collins2, Jo Bradwell3, Chris Imray1, Tim Clarke1, Steve Brearey4, John Miles1. Birmingham Medical Research, Expeditionary Society1, ScanMed Medical Instruments1. colin@cpuchan.demon.co.uk.

Sildefanil (Viagra), a vasodilating selective phosphodiesterase inhibitor, has been noted to improve pulmonary oedema at altitude. We investigated the cerebrovascular response to sildefanil with respect to blood flow and oxygenation at altitude. Methods: 6 male subjects (age 34–60 years) were studied 2 days after arrival at 3455m. Baseline measurements of right earlobe SaO2 were obtained. Sildenafil (25mg) was administered orally and repeat measurements made at 1 hours. PaO2 increased by 1–2 mmHg, regulated the breathing pattern, left end tidal FO2 unchanged at 0.12 and increased SaO2 to 87%. O2 flow of 1.2 L/min, (i.e., deperting the tank at 0.7 L/min at 1A) was maintained overnight increasing end tidal FO2 to 0.27 and SaO2 to 94%. In the morning the treatment was discontinued; the patient remained well without O2 supplementation for about 2–3 hours while preparing for descent. Conclusions: This breathing system effectively improves SaO2 by eliminating periodic breathing. It efficiently delivered O2 at high altitude. This portable circuit can be configured for use in the field.

DAILY OXYGEN DESATURATION AND PULMONARY HYPERTENSION IN MODERATE-SEVERE COPD WITHOUT SEVERE HYPOXEMIA AT REST.

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Pulmonary hypertension can develop in COPD patients, usually due to chronic hypoxemia. Some patients present PH even in the absence of severe resting hypoxemia. Little is known about oxygen status during day and night in these patients. We aimed to study 24hrs monitoring of SaO2 in moderate-severe COPD with resting PaO2 >60mmHg and correlate the presence, duration and severity of oxygen desaturations (Des) to PAP value. 20 stable moderate-severe COPD patients were enrolled. Respiratory function tests (RFT), blood gas analysis, 6 walking tests (WT), 24hrs monitoring of SaO2, non invasive evaluation of PAP were performed. Des are defined as SpO2 falls > 4%. RESULTS mean (SE): Age 69±1.6, FEV1 42±6.3, VC 867±5.9, PaO2mmHg34±(2.4), PaCO2mmHg79±(1.6), PaO2mmHg 39±(9.9), DLco 47±(5), packs/year 56±(7.4). A positive correlation has been found between PAP and duration of Des. When the patients were classified into 2 groups using PAP ≥ 35mmHg as cut-off (10 high PAP ≥35mmHg (H-PAP), 10 low PAP <35mmHg (L-PAP)) we found significant difference (p < 0.05) only for the duration of daily Des expressed as % of total daily time: in H-PAP 7.3±(2.6) in L-PAP 1.0(5.2) and the presence of Des during WT. In H-PAP group 9/10 pts had WT Des compared to 3/10 in L-PAP group (p < 0.05). RFT, resting BGA, severity of Des were not different. We conclude that the observation of oxygen status during daily activities should carefully be examined in COPD patients without severe resting hypoxemia together with the PAP evaluation.

INHIBITION OF PHOSPHODIESTERASE-5 IN ADDITION TO INHALED NITRIC OXIDE COMPLETELY INHIBITS HIGH ALTITUDE ASSOCIATED PULMONARY VASOCONSTRICTION.

Swenega, Agostini, Patrick jg, Manuel Beeler, Oliver Senat, Rachel Thalman1, Rolf Jenni, Konrad Bloch, Hans Peter Brunner-La Rocca. Medical ICU, Univ Hospital Zurich, Switzerland1, Medicine, Hospital Samedan, Switzerland2, Pneumology, Univ Hospital Zurich, Switzerland3, Cardiology, Univ Hospital Zurich, Switzerland4, Cardiology, Univ Hospital Basel, Switzerland5. klinmax@hsc.unizh.ch.

Inhibition of phosphodiesterase-5 in addition to inhaled nitric oxide completely inhibits high altitude associated pulmonary vasoconstriction. Endogenous nitric oxide (NO) synthesis and/or phosphodiesterase-5 activity is probably crucial for regulation of hypoxic pulmonary vasoconstriction at high altitude. Therefore, 22 healthy non-acclimatized mountaineers were investigated using Doppler-echocardiography at low altitude (LA) (490 m) and after rapid ascent (within 24 hours) to 4559 m. Three hours after arrival systemic pulmonary artery pressure (sPpa) was measured during NO-inhalation and 90 min after 50 mg sildenafil, first without, and then with NO (HA1). Baseline measurements were repeated the following morning before descent (HA2). Eleven of the 22 subjects developed acute mountain sickness (Lake Louise score > 5), but none high altitude pulmonary edema (HAPE). Four had a previous episode of HAPE. Mean (±SD) arterial oxygen saturation (SaO2) was 97 ± 1% at LA, and 75 ± 4% and 78 ± 3% at HA1 and HA2, respectively (p < 0.001). StPpa, estimated from the tricuspid regurgitation, was on average 27 ± 5 mmHg at LA, and 44 ± 10 mmHg at HA1 and 42 ± 8 mmHg at HA2 (p < 0.001). Sildefanil and NO combined decreased sPpa from 44 ± 10 mmHg to 32 ± 6 mmHg, 33 ± 6 mmHg and 28 ± 5 mmHg, respectively (p < 0.001). Sildenafil and NO combined decreased sPpa to LA level (p = 0.16). Mean blood pressures before and 90 minutes after sildenafil were identical (87 ± 7 vs. 87 ± 6 mmHg). We conclude that inhibition of the phosphodiesterase-5 decreases Ppa as effectively as NO without causing systemic hypotension, and that only the combination of both completely inhibited high altitude associated pulmonary vasoconstriction, which supports the role of both, endogenous NO-synthesis and phosphodiesterase-5 activity, in hypoxic pulmonary vasoconstriction at high altitude.

THE EFFECT OF SILDEFANIL (VIAGRA) ON CEREBRAL HAEMODYNAMICS AT ALTITUDE.

Colin Chan1, Phil Collins2, Jo Bradwell3, Chris Imray1, Tim Clarke1, Steve Brearey4, John Miles1. Birmingham Medical Research, Expeditionary Society1, ScanMed Medical Instruments1. colin@cpuchan.demon.co.uk.

Sildefanil (Viagra), a vasodilating selective phosphodiesterase inhibitor, has been noted to improve pulmonary oedema at altitude. We investigated the cerebrovascular response to sildefanil with respect to blood flow and oxygenation at altitude. Methods: 6 male subjects (age 34–60 years) were studied 2 days after arrival at 3455m. Baseline measurements of right earlobe pulse oximetry, continuous non-invasive blood pressure monitoring, transcranial Doppler of the right middle cerebral artery and near infrared cerebral oxygen saturation were performed. 50 mg of sildefanil was then administered orally and repeat measurements made at 1 hours. Paired t test was used for statistical analysis with a p value < 0.05 considered as being statistically significant. Results: Conclusion: Although sildefanil appears to reduce cerebral blood velocity at 3455m, there is a small but significant increase in cerebral oxygenation on infrared spectroscopy. This is associated with a rise in pulse rate but without any appreciable change in either blood pressure or peripheral oxygen saturation. This may imply that the potential benefit of sildefanil at altitude may be due to its influence on the cerebral vascular bed in addition to its pulmonary effects.
EPIDEMIOLOGICAL MODELS OF ACUTE MOUNTAIN SICKNESS (AMS).
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AMS commonly occurs at altitudes exceeding 2,500 m and usually resolves by acclimatization if further ascent is modest or avoided. We modeled AMS with data from a previous study of 302 trekkers recruited as they arrived at 3,840 m during hikes through altitudes of 1,500–6,200 m (Murdoch DR, ASEM 66:148, 1995). Based on self-reported symptoms, we estimated AMS Scores (Hackett scale) by linear regression and the probability of a positive AMS Diagnosis (Lake Louise criteria) by logistic regression. As rapid ascent is implicated with increased AMS risk, we estimated the maximum AMS probability (P(AMS)) that occurred in three recommended ascent regimens to 5,300 m: (a) 600 m/day beyond 2,500 m with a rest day every 600 m; (b) 300 m/day beyond 3,000 m until 4,200 m and 300 m every two days beyond 4,200 m; and (c) 150 m/day beyond 2,750 m with two days at 4,250 m followed by ascent at 150 m/day to 5,450 m with two rest days. Variables significantly associated with either Score or Diagnosis (but not always both) included gender, age, acetazolamide, altitude, exposure day, change in altitude on prior days, and Score on prior days. AMS probability decreased with age (Odds Ratio, OR = 1.18 per decade) and acetazolamide (OR = 3.55). Females were more susceptible than males (OR = 1.51). The maximum estimated P(AMS) associated with the recommended ascent regimens were 0.17, 0.14 and 0.06 at 5,300 m, respectively. Comparisons with data from the literature suggested that our estimates of AMS Score and probability underestimated the true values, probably because our subjects were partly acclimatized upon entering the study. Epidemiological models might be useful for testing hypotheses concerning AMS and for planning low risk ascents when calibrated with data from unacclimatized subjects.

HIGH ALTITUDE RESEARCH HAWAII.
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High altitude research is difficult due to isolated locations with extreme environmental conditions. We are in the early stages of developing high altitude research at the Mauna Kea Summit (4205m). A primary concern in this initial effort was to establish broadband connectivity to the summit for the real-time transfer of physiologic and other data. The summit’s location has several advantages. Hilo Airport is a major inter-island airport for commercial jet aircraft, and is a short flight away from Honolulu International Airport. Travel to the summit from the airport (and sea level) is a 90-minute drive over good roads, with snow being an infrequent factor. A hospital is 60 minutes away. Hale Pohaku (2800m) is 20 minutes from the summit, and serves as the main support area for lodging and logistics. It is ideally situated to acclimatize and support staff and subjects. The summit’s main research building accommodates up to 25 people, with the lack of plumbing being the only negative. The building has been wired with 2 phone lines and broadband IP connected to the Univ Hawaii’s network with a DS3 connection. We successfully accomplished transfer of multiple types of data outside of the Univ network to Honolulu and Stanford Univ. Data consisted of the following: live streaming physiologic data using NASA-Stanford developed systems (pulse oximetry, 2-lead EKG, heart rate, respiratory rate), live video teleconferencing, live audio from a digital stethoscope, and transmission of x-ray images. The Mauna Kea Summit is an ideal site for a high altitude research laboratory due to its unique location, good facilities, and broadband connectivity. With further development, we hope to open Mauna Kea as an international site for high altitude research.

ACUTE MOUNTAIN SICKNESS IN ADOLESCENTS.
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Aims Increasing numbers of adolescents travel to high altitude with school expeditions. This study aimed to determine the incidence of AMS in adolescents at altitude, and the practicalities of using the adult Lake Louise questionnaire in this age group. Methods Twelve teenagers aged 15–18 years (7 male) traveled for 21 days between 2,400m–5,200m. Daily questionnaires were completed. Group leaders (non-medical) were informed about any subject with a score ≥ 3. Treatment/descent was then determined. Results All 12 subjects completed the questionnaires as requested (100%). 11 subjects suffered from AMS, 1 subject was evacuated to a lower altitude. The mean cumulative AMS score was 27.3 (range 0–53). Females appeared to have more minor symptoms over a longer time course, whereas males appeared to have more severe symptoms over a shorter time course. Conclusions The largest UK tour operator for this age group advocates that all travelers are given prophylactic acetazolamide above 3000m. The approach raises serious concerns: unnecessary drug use, drug side effects, subsequent restricted therapeutic options, and potential lack of awareness of AMS. This study demonstrates that a motivated group of adolescents are capable of self-monitoring for AMS. Combined with an appropriate ascent profile and support we feel this approach is safer and more appropriate.

DOES ACUTE MOUNTAIN SICKNESS INFLUENCE LACTATE METABOLISM AT HIGH ALTITUDE?
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The field of lactate metabolism at high altitude has perplexed physiologists, namely due to observations that post-exercise blood lactate is increased on arrival at altitude, but paradoxically decreases with acclimatization, despite maintained hypoxia and no change in oxygen delivery. Such high altitude studies have primarily involved the use of highly fit individuals as test subjects. It is possible that the results of these studies may reflect the level of training of the subjects. To investigate the role of subject selection on energy metabolism at high altitude, twelve male subjects were selected to display a broad range of fitness levels, from the power trained individual (VO2max 39.4 ml/kg/min) to the elite endurance athlete (VO2max 66.5 ml/kg/min). Throughout a three week acclimatization at the White Mountain Research Station (3,800m), a series of maximal and submaximal (70% relative VO2max) exercise tests were performed and blood samples were collected to monitor plasma lactate concentration during exercise and recovery. All subjects completed the Lake Louise Acute Mountain Sickness (AMS) Questionnaire during the first five days at altitude. As a group, the subjects did not display any significant trends in lactate levels between test trials (post-acclimatization). However, four subjects exhibiting symptoms of AMS and at the lower end of the fitness spectrum (poor responders, age 25±3 years, body mass 78.4±15.3 kg, VO2max 48.2±7.8 ml/min/kg) did display significantly lower lactate levels at submaximal workloads after 3 weeks of acclimatization compared to samples taken during hypoxia. Also, peak post-exercise lactate concentrations were significantly different between the good responders (age 25±3 years, body mass 75.2±12.2 kg, VO2max 58.1±6.6 ml/min/kg) and poor responders during acute hypoxia testing. The results of this study suggest that AMS scoring and fitness level should be considered when analyzing metabolic data.
93. **ALTIMETRIC RESIDENCE AND ARTERIAL OXYGEN SATURATION ARE INDEPENDENT RISK FACTORS FOR AMS AT THE KILIMANJARO.**

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Little is known about the risk factors predisposing to the development of acute mountain sickness (AMS) in climbers going to the summit of the Kilimanjaro. Therefore, we investigated, using the Lake Louise score protocol, 204 climbers, 76 women and 117 men, (mean age 35 years) staying overnight at the Kibo hut (4700m). Climbers reached this altitude between day 3 and 4 of their trek. A multivariate logistic regression analysis was performed for the following possible AMS risk factors: age, sex, body mass index (BMI), AMS history, altitude of residence, acclimatization days (sleep at an altitude > 2500m) during previous 3 months, medication intake during expedition and arterial oxygen saturation (SaO2). Our analysis revealed that an SaO2 < 81% (p = 0.007) and a residence at an altitude of < 700m (p = 0.038) were independent risk factors for the development of AMS. In females, but not in males, the use of a malaria prophylaxis was an independent predictor for less AMS (p = 0.024). The prevalence of AMS was 22% (15/67) vs. 45% (25/55) in climbers with a SaO2 < 81% (p = 0.007), 15% (3/20) vs. 39% (66/171) in those living ≥ 700m and 21% (8/37) vs. 47% (19/40) (p = 0.039) in females taking malaria prophylaxis. Univariate analysis showed a trend for a decreased incidence of AMS in climbers taking acetazolamide (p = 0.039) in females taking malaria prophylaxis. Univariate analysis showed a trend for a decreased incidence of AMS in climbers taking acetazolamide (p = 0.039) in females taking malaria prophylaxis. Univariate analysis showed a trend for a decreased incidence of AMS in climbers taking acetazolamide (p = 0.039) in females taking malaria prophylaxis. Univariate analysis showed a trend for a decreased incidence of AMS in climbers taking acetazolamide (p = 0.039) in females taking malaria prophylaxis. Univariate analysis showed a trend for a decreased incidence of AMS in climbers taking acetazolamide (p = 0.039) in females taking malaria prophylaxis.

94. **PREVALENCE OF ACUTE MOUNTAIN SICKNESS AMONG TOURIST CLIMBING KILIMANJARO.**

Phillip Widmer, Patrizia Demond, H Marty, Marco Maggiorini. Univ Bern, Switzerland, Medical ICU, Univ Hosp Zurich, Switzerland. klimmax@usz.unizh.ch.

Treking expeditions to the Kilimanjaro are popular, however, prevalence of acute mountain sickness (AMS) is unknown. Therefore, using the Lake Louise AMS protocol at the altitude of 2700m, 3700m and 4700 m we assessed the prevalence of AMS before dinner and the following morning. A total of 269 climbers, 94 women and 174 men, (mean age 36 years, range 13–76 years) were interviewed during their ascent to the summit. According to the Lake Louise AMS definition (score ≥ 5 points) the prevalence of AMS before dinner was 12.3% at the altitude of 3700m and 18% at 4700m (p < 0.01). The mean Lake Louise score being 1.9 ± 1.9 at 3700m and 2.9 ± 2.5 at 4700m (p < 0.05). After overnight rest, a total score of ≥ 5 points in the self-assessment section (SAS) of the protocol was found in 3.6% of the climbers at 2700m, 4% at 3700m and 36.4% at 4700m (p < 0.01). During overnight rest the percent of climbers with a SAS score of ≥ 5 decreased by 3.1% at 3700m (p < 0.05) and increased by 18.8% at 4700m (p < 0.01). Sixty-six climbers reached the altitude of 4700 on day 3 and 135 on day 4. In these two groups, the morning SAS score was ≥ 5 in 35.4% and 37.7% of the climbers, respectively (p = ns). We conclude that, compared to similar altitudes in the Alps, the prevalence of AMS at the Kilimanjaro is slightly lower, this probably because of a slower rate of ascent. The prevalence of AMS symptoms was not different whether the summit was climbed on day 4 or 5. Overnight rest improved AMS symptoms at the altitude of 3700, but worsened it at the altitude of 4700m.

95. **ACUTE ALTITUDE EXPOSURE ALTERS PUPIL BUT NOT OCULOMOTOR REFLEXES.**


Unlike visual function, the effects of hypoxia on oculomotor and pupil reflexes have not been well defined. In order to determine the effects of acute altitude exposure, initial pupil diameter (IPD), constriction amplitude (CA), constriction latency (CL), and saccadic velocity (SV) were measured in 26 (25 ± 8 yr, mean ± SD) and 9 women (29 ± 11 yr) before and after a 2.5-hr decompression to 459 mmHg (13,318 ft). After <1hr, IPD and CL were reduced (6.0 ± 1.0 to 5.7 ± 1.0 mm, p = 0.003 and 302 ± 28 to 296 ± 27 msec, p < 0.001, respectively). No gender differences were obtained. To determine the possible effect of hypobaria, 18 men (25 ± 5 yr) were driven to the summit of Pikes Peak (14,110 ft, 463 mmHg) over 1.5 h while breathing O2. Measurements were made immediately, with and without O2, after reaching the summit and 3 h later. Hypobaria had no effect on any of the measured variables, i.e., results obtained with O2 at altitude were not different from those at sea level. Pikes Peak results were qualitatively similar to those obtained with simulated altitude, but temporally delayed: IPD (O2 <1 h: 5.9 ± 0.8; no O2, 3 h: 5.2 ± 1.0 mm, p < 0.001), and CL (O2 <1 h: 302 ± 19; no O2, 24 h: 286 ± 19 msec, p < 0.001). Reductions in CA were also obtained after 24 h (1.2 ± 0.4 vs. 1.0 ± 0.3 mm, p = 0.02). No SV changes were obtained in either environmental condition. Hypoxia-induced reductions in pupil reflexes are reproducible, objective, and time dependent and may be a harbinger of subsequent altitude-induced illnesses and an index of acclimatization.

96. **INFLUENCE OF MODERATE ALTITUDE RESIDENCE ON ARTERIAL OXYGEN SATURATION AT HIGHER ALTITUDES.**


The purpose of this study was to compare the distribution of arterial oxygen saturation (SaO2) and subjective symptoms to hypoxia in moderate altitude residents (MAR) and low altitude residents (LAR) following rapid ascent to 4,056 m (pressure altitude). Resting ventilatory parameters (open-circuit spirometry) and SaO2 (pulse oximetry) were measured in 38 volunteers (25 men, 13 women) residing for >3 months near Colorado Springs, CO (MAR group). These measurements were made at 1,940 m (US Air Force Academy) and after ~1hr at 4,056 m on the summit of Pikes Peak, CO following ascent by car. Resting SaO2 was also measured at 610 m elevation intervals during the ascent. The LAR group of 39 volunteers (30 men, 9 women) were exposed to a similar ascent profile in a hypobaric chamber. Results (X ¯ ± stephen.muza@na.amedd.army.mil.) differed in the self-assessment section (SAS) of the protocol was found in 3.6% of the climbers at 2700m, 4% at 3700m and 36.4% at 4700m (p < 0.01). During overnight rest the percent of climbers with a SAS score of ≥ 5 decreased by 3.1% at 3700m (p < 0.05) and increased by 18.8% at 4700m (p < 0.01). Sixty-six climbers reached the altitude of 4700 on day 3 and 135 on day 4. In these two groups, the morning SAS score was ≥ 5 in 35.4% and 37.7% of the climbers, respectively (p = ns). We conclude that, compared to similar altitudes in the Alps, the prevalence of AMS at the Kilimanjaro is slightly lower, this probably because of a slower rate of ascent. The prevalence of AMS symptoms was not different whether the summit was climbed on day 4 or 5. Overnight rest improved AMS symptoms at the altitude of 3700, but worsened it at the altitude of 4700m.
Non-invasive estimation of arterial oxygen saturation (SpO₂) with pulse oximetry has been identified as a possible method to assess the pathology of acute mountain sickness (AMS) during sojourns to high altitude. In order to evaluate the performance of pulse oximetry and address the basic efficacy of normobaric hypoxic chambers (NHCh), direct measurements of arterial oxygen saturation (SaO₂) by cooximetry (AVOXimeter 4000), were simultaneously compared with SpO₂ (Nellcor 295) using both reflectance (RS-10) and transmission (D-25) sensors (placed on the forehead and finger respectively), while the inspired oxygen fraction (FIO₂) inside a NHCh (Hypoxico Inc.) was progressively reduced from .209 to .115 over a 2.5hr period. A catheter was placed in the radial artery of thirteen subjects (seven females and six males) which provided eighty-four data points over the hypoxic range. To monitor subject health status, the Lake Louise AMS self-assessment questionnaire was completed every half hour for evaluation of altitude illness like symptoms. Within Subject analyses MANOVA exhibited a significant time effect for SaO₂ during the progressive normobaric hypoxic exposure (F(4,44) = 97.93, P < 0.0001) (Table). As well, a significant time effect was observed in AMS symptomatology (F(3,33) = 13.51, P < 0.001). No significant interaction was observed between factors. It was found at standard altitude that all participants expected that pulse oximetry provides defendable accuracy for estimating SaO₂ during NHCh exposures, although site specificity of the sensor may be a factor, especially as the severity of hypoxemia progresses. For example and in summary, this data set suggests that in response to progressive normobaric hypoxia, the performance of finger tip pulse oximetry deteriorates substantially at saturation levels below 85% when compared to the forehead position.

EFFECTS OF ACUTE MOUNTAIN SICKNESS SYMPTOMS ON ENERGY INTAKE: RESULTS FROM A TYPICAL HIMALAYAN TREK TO MAKALU BASE CAMP.

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High altitude induced body weight changes are in part due to a disequilibrium between energy intake and energy expenditure. Acute mountain sickness (AMS) symptoms seem to be primarily responsible for the reduction of energy intake. The main goal of this research was to investigate the effects of AMS symptoms on energy intake (EI) and macronutrient distribution in healthy humans (aged 43 ± 11 yr and BMI 24.5 ± 4.1kg/m2) during a typical Himalayan trekking situation. The maximum altitude reached was 5200m. 24 h dietary recalls and AMS symptoms were recorded on all days of the trek. Subjects were eating ad libitum and took part in a 6-day climb below 2500m (low altitude: LA1), followed by 8 days above 2500m (high altitude: HA) and a 5-day descent below 2500m (low altitude: LA2). Results showed a decrease of mean caloric intake between LA1 and HA (3263 ± 821 vs 2723 ± 838 Kcal/d, respectively; p < 0.05) while energy intake during LA2 (3706 ± 801 Kcal/d) was significantly higher than energy intake during LA1 (p < 0.05) and HA (p < 0.001). No specific modifications in macronutrient distribution intake were observed. As expected, AMS symptoms were greater during HA than during LA1 and LA2 (p < 0.05). Despite a parallel increase of AMS with the decrease in energy intake observed when comparing LA1 to HA values, no significant association was observed between changes in AMS symptoms and changes in energy or macronutrient intakes. In conclusion, HA was associated with a decrease of energy intake, which did not seem to be macronutrient specific and with an increase in AMS symptoms, while the return to LA2 was accompanied by an overcompensation of energy intake and a reduction of AMS symptoms under the conditions described in this study.

METHOD COMPARISON R2 Slope Intercept Bias Precision 95%CI
SaO₂ vs SpO₂(RS-10) 0.9199 1.0031 -7.3280 0.016 2.47 -5.41 to 4.47
SaO₂ vs SpO₂(D-25) 0.85 1.0182 -5.51 0.1 0.47 -6.52 to 5.58
SaO₂ vs SaO₂(RS-10) <0.05 <0.02 0.8018 0.018 0.37 0.024 -0.004 to 1.08
SaO₂ vs SaO₂(D-25) <0.05 <0.02 0.5646 1.190a -15.9989 1.17 4.34 -7.55 to 9.81

Validations of Pulse Oximetry During Progressive Normobaric Hypoxia Utilizing Portable Chamber.

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NO EVIDENCE OF VASOGENTIC BRAIN EDEMA IN SEVERE ACUTE MOUNTAIN SICKNESS.

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It was hypothesized that the symptoms of acute mountain sickness (AMS) were caused by cerebral vasogenic edema with AMS therefore an early, benign stage of high altitude cerebral edema (HACE). Thus, we investigated the presence of vasogenic edema in severe acute mountain sickness with diffusion weighted magnetic resonance imaging and evaluated the changes of inner cerebrospinal fluid volumes (iCSF) as indicator of brain swelling. In a randomized, double-blind cross-over trial 10 subjects were exposed for 10 h to a simulated altitude of 4500 m for three occasions, either taking placebo, acetazolamide (250 mg bid) or theophylline (250 mg bid). T2 weighted images and diffusion weighted magnetic resonance imaging were obtained directly after altitude exposure under hypoxic conditions. Although nine of ten subjects had moderate to severe AMS (median Lake Louise Score 6.0), we found no indication of vasogenic edema, irrespective of the medication taken. In all subjects, we found a significant decrease in inner cerebrospinal fluid volumes (median reduction with placebo 10.3%, with acetazolamide 13.2%, with theophylline 12.2%, p > 0.05), indicating brain swelling. There was no correlation between AMS symptoms and fluid shift. However, we found a significant positive correlation of large iCSF and more severe AMS under placebo conditions (r = 0.76, p = 0.01). We conclude that vasogenic edema is not present in moderate to severe AMS.

GINKGO BILOBA DECREASE ACUTE MOUNTAIN SICKNESS (AMS) AT 3700 M.

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Ginkgo biloba (Gb) have two mechanisms that could be considered in the reduction of AMS: enhance cerebral circulation and have a powerful antioxidant action. Previous studies suggest that 5 days of prophylactic treatment with Gb (120 mg/12 h) decrease AMS at 4205 m, in contrast other study shown a decrease of AMS with treatment of Gb 24 h previously (60 mg/12 h). Objective: Determine effect of prophylactic treatment (Gb 80mg/12 hrs, 24 h before to ascend and treatment maintained) in subjects without experience to high altitude of 3700 m. Subjects: 32 participants residing at sea level were transported from sea level to 3700 m (Ollague). Methods: Three groups: a) ginkgo biloba (n = 8) received 80 mg/12 hrs; b) acetazolamide (n = 12) 250mg/12 h, and c) placebo (n = 12), 24 hrs before to ascend, start the treatment and was maintained during exposure to high altitude. The Lake Louise Questionnaire constituted the primary outcome measure at baseline, in the morning at 3700 m by 2 days; AMS was defined as a Lake Louise Self-Report Score (LLSR) > 3. Oxygen saturation and arterial pressure were simultaneously measured at all sampling of AMS. Results: A significant reduction of AMS was observed in the group that received Gb (0%, p < 0.05) in comparison with acetazolamide (34.5%, p < 0.05) and placebo (54%). No differences were observed in oxygen saturation in Gb (91 ± 1) versus acetazolamide (89 ± 1) groups but a major oxygen saturations in comparison with the placebo (84 ± 1, p < 0.05). No differences were observed in the mean arterial pressure. Conclusion: This study further supports the use of Gb in prevention of AMS. This is the first study to corroborate that 24hr pre-treatment with Gb and with maintenance during exposure to high altitude is sufficient to reduce the incidence of AMS in subject without experience. Airliquide-Chile; VRA-UDP.
Wobble Board (WB) Acute Mountain Sickness (AMS) and Cerebral Regional Oxygenation (SPO2).

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We have described previously (High Altitude Medicine & Biology 2; 104: 2001) a quantitative test of unsteadiness recording the number and duration of contacts per minute of a wobble board to a horizontal metal base plate. Results showed a relationship with AMS in older subjects but the test was not sufficiently sensitive in younger subjects. We have modified the board with a smaller diameter ball between the board and the recording plate and measured 23 healthy subjects ascending to 5260m. Results have been related to Lake Louise AMS scores, the Sharp-ened Romberg Test (SRT) of ataxia and to cerebral regional oxygenation (rSO2) measured at the same altitude. WB improved over 17 d of the expedition from mean 14.8, 12.9secs at sea level, to 10.4, 8.7secs at 3610m, to 8.7, 7.3secs at 4750m and 6.4secs at 5260m. In the 19 subjects with full data at 5260m, WB scores did not correlate with the AMS scores (r = 0.3 ns) nor with the SRT (SRT normal AMS score 7.2 +/−3.7sd. SRT abnormal AMS 8.8 +/−7.6 ns) nor with rSO2 (r = −0.3 ns). We conclude that this more sensitive WB is not a useful clinical measure of ataxia. In the small numbers studied WB results were not a useful measure of AMS and did not correlate with cerebral regional oxygenation. It is not a practical test for an ill subject and requires time to learn.

Efficacy of Low Dose Acetazolamide (125 MG BID) for the Prophylaxis of Acute Mountain Sickness.

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Objective: To determine the efficacy of low dose acetazolamide (125 mg twice daily) for the prevention of acute mountain sickness (AMS). Methods: A prospective, double blind, randomized, placebo-controlled trial was carried out in the Mt. Everest region of Nepal between Shericho (4243m), the study enrollment site and Lobuje (4937m), the study endpoint. The participants were 197 healthy male and female trekkers of diverse background and they were evaluated with the Lake Louise Acute Mountain Sickness Scoring System and pulse oximetry. The main outcome measures were incidence and severity of AMS as judged by the Lake Louise Questionnaire score at Lobuje. Results: There were 197 participants enrolled, and 155 returned their data sheets at Lobuje. In the treatment group there was a statistically significant reduction in incidence of AMS (placebo group: 24.7%, 20 out of 81 subjects and acetazolamide group, 12.2%, 9 out of 74 subjects). Prophylaxis with acetazolamide conferred a 50.6% relative risk reduction, and the number needed to treat in order to prevent one instance of AMS was 8. Of those with AMS 30% in the placebo group (6 of 20) vs. 0% in the acetazolamide group (0 of 9) experienced a more severe degree of AMS as defined by a Lake Louise Questionnaire score of 5 or greater (p = 0.14). Secondary outcome measures associated with statistically significant findings favouring the treatment group included decrease in headache and a greater increase in final oxygen saturation at Lobuje. Conclusion: Acetazolamide 125 mg twice daily was effective in decreasing the incidence of AMS in this Himalayan trekking population.

Acute mountain sickness (AMS) is not usually accompanied by abnormal neurological findings and the development of truncal ataxia indicates progress of AMS to high altitude cerebral edema (HACE). Ataxia measured by the heel-toe walking test is one of the signs recommended in the Lake Louise AMS score. The Sharpened Romberg Test (SRT) of ataxia is widely used to assess divers with decompression sickness and is a quantitative measurement. In the test the subject stands on a flat surface, feet aligned in strict tandem heel-toe position, with arms crossed so that the hand falls on the opposite shoulder, the body is erect and the eyes shut. Subjects try to maintain this position for 60 seconds. If they fail the test is repeated for up to four attempts. Scoring is based on the cumulative time of the four trials up to a maximum 240 seconds. The relative usefulness of both tests of ataxia was evaluated in 20 healthy subjects ascending to 5260m. At 3610m SRT was normal (240secs) in 10 subjects (AMS score 1.9 +/−2.0sd) and abnormal (<240secs) in 10 subjects (AMS score 2.7 +/−3.6 NS). At 5260m SRT was normal in 12 subjects (AMS score 2.4 +/−2.0) and abnormal in 8 subjects (AMS score 4.1 +/−1.6 p < 0.05). Heel-toe testing at the same times showed only four abnormal results at 3610m and one at 5260m. We conclude that the SRT is simple to perform and can be quantified. The test is more sensitive than the heel-toe test and relates to AMS scores at high altitude.

Methods:

A prospective, double blind, randomized, placebo-controlled trial was carried out in the Mt. Everest region of Nepal ... The main outcome measures were incidence and severity of AMS as judged by the Lake Louise Questionnaire score at Lobuje. The present study examined whether free radical-mediated vascular damage would influence individual susceptibility to acute mountain sickness (AMS). Methods: Twenty four subjects were examined at sea-level (SL), within 2–3h after an active ascent from 3,200m to 4,559m (HA1) ... (CPK) and cerebral [neuron-specific enolase (NSE)] vascular damage and various proinflammatory cytokines (IL-1b, IL-6, TNF-a and TNF-a pR-60). Results: AMS score increased markedly at HA (0.1 ± 0.3 points at SL, P < 0.05 vs. 4.6 ± 3.0 at HA1, 5.6 ± 3.3 at HA2 and 3.5 ± 2.8 at HA3). Fourteen subjects were diagnosed with clinical AMS (LL score > 5 points) and of these, 4 developed HAPE. While a general increase in CPK and TNF-a pR-60 was observed at HA (vs. SL, P < 0.05), retrospective analyses demonstrated no selective differences in these or any other metabolites between those with AMS compared to those who remained apparently healthy. Pooled data demonstrated an association between the magnitude of increase in NSE at HA1-3 and AMS score (r = 0.25, P < 0.05). Conclusions: The present findings demonstrate selective damage to skeletal muscle at HA that was independent of free radical-mediated peroxidative or inflammatory phenomena. Furthermore, increased free radical-mediated vascular damage does not appear to be a cause or consequence of AMS. While not establishing cause and effect, the association between AMS and NSE, an established marker of molecular damage to the blood-brain barrier, warrants further investigation.
105. DIRECT EVIDENCE FOR LIGHTNING-INDUCED FREE RADICAL GENERATION AND SKELETAL MUSCLE DAMAGE.
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Introduction: The present case-study examined changes in peripheral markers of free radical metabolism and skeletal/myocardial muscle damage 30th after a mountaineer had survived a direct lightning strike at 4,200m. Pre-exposure sea-level (normoxic control) data were available for comparative purposes. Control measurements were also obtained after simulated exposure to the combined stresses of inspiratory hypoxia and physical exercise in an environmental chamber. This provided an unique opportunity to examine metabolic sequelae caused directly by the lightning strike.
Methods: Venous blood was assayed for molecular markers of skeletal [myoglobin and total creatine phosphokinase (CPK)] and myocardial [cardiac troponin I (cTnI)] muscle damage. Ex vivo spin-trapping with (phenyl-tert-butylnitrone (PBN) combined with electron paramagnetic resonance (EPR) spectroscopy was incorporated for the direct detection of free radicals. The simulation study involved passive and active exposure to graded normobaric hypoxia (FiO₂ of 0.21 at sea-level to 0.13 at the summit) incorporating treadmill ascent and descent rates of 2.5m/min (applying a +50° gradient) and 3.8m/min (~50°) respectively.
Results: Compared to normoxic control data, the EPR signal intensity of the venous PBN adduct, myoglobin and CPK in the “lightning blood” was markedly greater than the increases observed following the simulation study. In contrast, no changes were observed in the peripheral concentration of cTnI. A marked decrease in the PBN adduct, myoglobin and CPK was observed within 2h following oral administration of water and lipid soluble antioxidant vitamins.
Conclusions: These findings are the first to document lightning-induced free radical generation and selective damage to skeletal muscle in a high-altitude mountaineer. Furthermore, free radicals may contribute to the pathogenesis of lightning injury and dietary supplementation with antioxidant vitamins may attenuate associated vascular damage.

106. COMPARISON OF GINKGO BILOBA, ACETAZOLAMIDE, AND PLACEBO FOR PREVENTION OF ACUTE MOUNTAIN SICKNESS.
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Objective: To determine the effectiveness of Ginkgo biloba and low-dose acetazolamide versus placebo as a prophylaxis for acute mountain sickness (AMS). Methods: Fifty-nine subjects volunteered for this double-blinded, randomized placebo-controlled study. All subjects resided at an elevation of 1370m to 1645m and had not been at higher altitudes for 2 weeks before the study. Subjects received ginkgo biloba 120mg, acetazolamide 125mg or placebo twice a day for 3 days prior to ascent and during altitude exposure. Subjects all ascended to 4300m over 2 hours by car in mid afternoon and stayed overnight. The Environmental Symptoms Questionnaire (ESQ-III short form) was completed before ascent and either after 24 hours at altitude or when removed from the study as a result of AMS. An ESQ-III of ≥ 0.7 and a Lake Louise Score of ≥ 1 with a headache present, was required for diagnosis of AMS. Results: acetazolamide reduced the incidence of AMS compared to placebo (3 of 22 vs 10 of 22 with AMS respectively).
Acetazolamide also reduced the severity of AMS (mean ESQ-III = 0.79 ± 0.68 vs. 0.34 ± 0.45, = 0.007, placebo vs. acetazolamide. Ginkgo tended to reduce both incidence and severity of AMS, but the difference was not statistically significant (mean ESQ-III = 0.79 ± 0.71 vs. 0.56 ± 0.59, = 0.07, placebo vs. ginkgo). Conclusion: Low-dose acetazolamide and ginkgo biloba taken 3 days prior to rapid ascent to 4300m reduced both incidence and severity of AMS. Ginkgo in this study, in contrast to our previous study at this altitude, did not reduce AMS. This might be because ginkgo was started 5 days before ascent in the previous study, but this and other possibilities require further study.

107. INTERLEUKIN-6 RESPONSE IN ACUTE AND CHRONIC HYPOXIA: ROLE OF EXERCISE INTENSITY.
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Recently it has been shown that plasma IL-6 concentration is increased during exercise in hypoxia (1), and that the increase was caused by augmented norepinephrine levels. However, since the response of IL-6 to exercise is intensity dependent, we hypothesized that if the workload is adjusted to match the same relative exercise intensity as at sea level, no changes in the IL-6 response would occur.
To test this, 8 Danish sea level residents were studied during a 60min exercise on a cycle ergometer (SL), in acute (AH) and chronic hypoxia (CH), at the same absolute (abs) and same relative (rel) exercise intensity. In AHs and CHs the IL-6 derived response to exercise increased as found by others. However, in AHrel and CHrel no changes in IL-6 response were found compared to sea level exercise. The changes found in IL-6 during AHs and CHs did not match changes in circulating catecholamine levels. We conclude that the plasma IL-6 concentration is exercise intensity dependent, and that factors other than catecholamines levels are important for its regulation.

108. BODY TEMPERATURE AUTONOMIC RESPONSES AND ACUTE MOUNTAIN SICKNESS.
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A few studies have reported increased body temperature (Tb) associated with acute mountain sickness (AMS), but these usually include exercise, varying environmental conditions over days and pulmonary edema. We wished to determine whether Tb would increase with AMS at sea level and whether it might be related to autonomic tone. The 94 exposures of 51 men and women to reduced Pb (423 mm Hg = 16,000 ft = 4,850 m) were carried out for 8–12 hr, with duration dependent on AMS symptoms. AMS was evaluated by LL and AMS-C scores at end of exposure and Tb of 0.2–0.9) and 16 other subjects with highest AMS scores (mean LL = 5–11; mean AMS-C = 2.7, range = 1.5–3.7) demonstrated a transient decline in Tb from A1 to A6 in AMS, in contrast to a rise in non-AMS (p = 0.001). Catecholamines, HR and HR variability (increased low F/high F ratio) indicated significant elevation of sympathetic activity in AMS, associated with the fall in Tb, but no change in metabolic rate. The apparently greater heat loss during early AMS suggests increased hypoxic vasodilation in spite of enhanced sympathetic drive. Greater hypoxic vasodilation and elevated HR in AMS in the absence of metabolic rate and ventilation changes may suggest that augmentation of ßadrenergic tone may be involved in early AMS pathophysiology. Supported in part by U.S. Army Med Res Materiel Cmd, DAMD17-96-C-6127.

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Methods: Subjects were exposed to environmental conditions approximating those on Mars and Mars-like planets. The protocol involved long-term observations of venous pressures at high altitude. The data show that a permanent exposure to high altitude (3,800 m) causes a transient increase in [EPO] and a combination of [Erythropoietin] and [Erythropoietin Receptor] levels in the blood of the subjects. The aim of the study was to elucidate either genetic/environment fitness or human diseases in subjects with different responses to hypoxia.

DOPAMINE (DA) D2- and D1-receptor (R) mRNA level modulation by hypoxia in the arterial chemoreflex pathway organs of 1 day old and adult rabbits.

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Dopamine (DA) D2- and D1-receptor (R) mRNA level modulation by hypoxia in the arterial chemoreflex pathway organs of 1 day old and adult rabbits. The aim of the study was to determine the effect of age on the pattern of hypoxia-induced changes of both DA D2- and D1-R mRNA levels in the carotid body (CB), petrosal ganglion (PG) and superior cervical ganglion (SCG). The mRNA levels were quantified by real-time PCR. The results show that hypoxia induced a significant increase in DA D2-R mRNA levels in the CB, PG and SCG, while the D1-R mRNA levels remained unchanged.


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The data show that a permanent exposure to high altitude (3,800 m) causes a transient increase in [EPO] and a combination of [Erythropoietin] and [Erythropoietin Receptor] levels in the blood of the subjects. The aim of the study was to elucidate either genetic/environment fitness or human diseases in subjects with different responses to hypoxia.
113. EFFECT OF BET A ADRENERGIC AND PARASYMPATHETIC BLOCK ON HEART RATE AND CARDIAC OUTPUT DURING EXERCISE IN NORMOXIA AND ACUTE HYPOXIA.
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Acute hypoxia increases heart rate (HR) and cardiac output (QT) at a given oxygen consumption (VO2) during submaximal exercise. The mechanism is widely believed to be increased sympathetic activation and circulating catecholamines acting on cardiac beta (β)-receptors. Recent evidence indicating a continued role for parasympathetic modulation of HR during moderate exercise, suggests a possible role for increased parasympathetic withdrawal in the increase in HR and QT during hypoxic exercise. To test this, we separately blocked the β sympathetic and parasympathetic arms of the autonomic nervous system (ANS) in 7 healthy subjects (6 M, 1 F; age = 31.7 ± 3.9 years, normoxic VO2max = 3.1 ± 0.7 l/min, means ± SD)—during exercise in normoxia and acute hypoxia (FiO2 = 0.125) to VO2max. Data were collected under 1) control conditions (CON), 2) after 8.0 mg propanolol IV and 3) after 0.8 mg glycopyrrolate IV, each on a different day. Cardiac output was measured using open circuit acec on breath-by-breath basis at 1100m, by sleeping either at 1100m (group C, n = 5) or in hypoxic rooms (group H, n = 5). It simulated altitudes of 2500m, 3000m and 3500m (3 ± 6 days). Lake Louise AMS score and arterial oxygen saturation (SaO2) during sleep were measured daily. Cardiac function (echocardiography) and ventilatory response to hypoxic exercise (HVRe, 30% normoxic VO2max) were evaluated at 1100m before and 15 days after the training session. RESULTS: Subjects did not complain of headache, gastrointestinal or dizzy symptoms. Fatigue and sleep disturbances were frequently mentioned but there was no significant difference between the two groups. In group H, interventricular septum thickness increased from 10.3 ± 0.8 to 11.2 ± 1.3 (p < 0.05), 4 out of 6 subjects showed a 5 to 10 mmHg increase in pulmonary arterial pressure. One subject showed a 6 mm increase in right ventricular end diastolic diameter. Mean nocturnal SaO2 at high altitude was 93.6, 91.7 and 89.8% at 2500, 3000 and 3500m, respectively. Three subjects showed a marked desaturation during the first two days after switching to a higher altitude (mean SaO2, 86% at 3500m). No significant changes were observed in HVRe or hypoxic exercise-induced desaturation 14 days after the training session. None of these parameters were correlated with the observed changes in performance (VO2max). CONCLUSION: sleeping during 18 days in hypoxic chambers (up to 3500m), while training at 1100m did not induce any significant clinical disorder; however cardiac morphological changes may occur as a result of prolonged increase in pulmonary pressure. Nocturnal saturation should be monitored to detect marked desaturation. Signs of ventilatory acclimatization had disappeared 15 days after the hypoxic exposure. This study was supported by grants from the International Olympic Committee and the French Ministry of Sports.
INTERVAL HYPOXIC TRAINING: TISSUE SPECIFICITY AND EFFECTIVENESS.
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It is necessary to study tissue specific effects of interval hypoxic training, to determine the most hypoxia sensitive organs, and to develop techniques preventing possible side effects. In our experiments we usually study the ratio of pro- and antioxidant factors in organs and tissues which is the prognostic criterion of changing their resistance to different environmental factors. It was observed that exposure to hypobaric hypoxia (2500 m, 6 hours daily for 30 days) results in a different reaction of the heart and liver of rats to such hypoxic training. In the heart, periodic activation of free radical oxidation is compensated by activation of antioxidant protective enzymes, the level of oxygen active forms not exceeding control, while in the liver, the sensitivity of tissue to oxidation induction increases in spite of such an activation of antioxidant system. The resistance of membrane structures after hypoxic training has changed as well. In the heart, the resistance of ion-transporting membrane systems to free-radical oxidation increases by 35-50%. At the same time, in the liver, the same exposure results in the 2-fold inhibition of plasmatic membrane Na-K-ATPase which is similar to the acute stress exposure. Thus, cardiomyocytes respond with compensatory effect to interval hypobaric training while hepatocytes are damaged. With lower intensity of hypobarian hypoxia (4000 m) the decrease of the enzymes level of the liver was decreased and disappeared completely at normobaric hypoxic training (21 daily sessions, one session included 12 hypoxic (10% O2) periods, 5 min each with 3 min reoxygenation). Our experiments revealed that such hypoxic training increased membrane structures resistance of the heart, liver and brain to the free-radical oxidation induction, to protease attack and other damaging factors. It means that normobaric hypoxic training is a mild adaptation exposure with "low cost" of adaptation and minimal risk of side effects.

HYPOBARIC HYPOXIA AS TRAINING OF SIBERIAN EXPEDITION EVEREST-2001 PARTICIPANTS.
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Research of effective methods to increase sportsmen's ability and improv their achievements is an important task in sport physiology. One of the more interesting methods is the adaptation to periodic hypobaric hypoxia. Our purpose was to devise a method of acceleration of high-altitude adaptation for participants of the Siberian expedition "Everest-2001" using hypobaric hypoxia training. Eight sportsmen (7 men and 1 woman) ages 30-52 old took part in experiment. The training process included 16 periods of hypobaric hypoxia over 50 days. The first "altitude" was 3500 m and the last "ascent" to 6400 m, rate of "ascent" was 10 m/s, and exposure time was 80 min. At "altitude" the sportsmen were tested with a velogrometer for 10 min. Each sportsman chose their own exercise load with none exceeding 300 W. Another important part of the training process was a special bioactive anti-oxidant food complex "ABISIB" (taken 3 times per day before eating). The following data were collected before and after the training course: antropometric measurements, ECG registration, analyses of blood and urine, PWC170, psychological tests by Lusher, Spilberger, Mini-mult etc. After the training course the sportsmen did exercises with a velogrometer at an "altitude" of 6400 m for 10 min without great effort, average PWC170 having increased 16% (p < 0.05). Two weeks later 6 sportsmen took part in "Everest-2001". They endured fast high-altitude adaptation (5200 m at once) successfully, 4 of them (3 men and 1 woman) reached the highest altitude, another sportsman became an active rescuer at 8300 m, and another was required to provide medical attention at 6400 m. Data obtained and interviews with each sportsman have demonstrated the efficiency of a training method using periodic hypobaric hypoxia and antioxidant food complex "ABISIB".

NOREPINEPHRINE MEDIATES RELEASE OF CORTICOTROPIN-RELEASING FACTOR IN HYPOTHALAMUS OF RATS DURING HYPOXIA.
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Norepinephrine (NE)-modulated CRF release in the hypothalamic paraventricular nucleus (PVN) of rats was studied in a simulated hypobaric chamber. NE, CRF and AVP were measured by HPLC and RIA. The results show that hypoxia equivalent to 5km for 24h and 7km for 30 min induced an increase of NE in the PVN by 117.20% and 24.33% respectively. NE in the central amygdala (ACE) was markedly increased at the same levels of hypoxia as well. A significant decrease of CRF in the median eminence (ME) of the hypothalamus was noted along with increases of NE in the PVN during hypoxia. Consequently, CAMP in the anterior pituitary and plasma corticosterone were increased significantly. Hypoxia induced not only reduction of CRF in the ME, but also in the PVN. However, CRF was not reduced in the ACE. In contrast with CRF, AVP in the ME exhibited a reverse alternation at 5km, but not at 7km hypoxia for 30 min. Hypoxia induced CRF release was reversed by treatment with prazosine, alpha-1-adreno-receptor antagonist, while further enhanced by yohimbine alpha-2-adreno-receptor antagonist. In conclusion, acute hypoxia stimulates, in an intensity and time-course dependent manner, NE release in both PVN and ACE, and consequently activates CRF release from the PVN and ME of the hypothalamus as well as corticosterone secretion. This effect is mediated by adrenergic alpha-1 and alpha-2 receptors.

CRF, NE, GLU, AND GC MODULATE GROWTH HORMONE AND PROLACTIN RELEASE IN RATS DURING HYPOXIA.
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Growth hormone (GH) and prolactin (PRL) release modulated by central corticotropin-releasing factor (CRF), norepinephrine (NE), glutamate (Glut) and glucocorticoids (GC) were studied in rats submitted to hypobarian hypoxia in a hypobaric chamber. Hypoxia (5 km for 1-7 d) suppressed body weight gains and reduced food intake (vs. control), effects which were prevented by a replacement of porcine GH (sc). After 5h simulated exposure to 5 km, the plasma GH was significantly decreased but pituitary GH increased markedly. The GH level in the pituitary was reduced during the hypoxia condition when rats were pre-treated with icv alpha-helical CRF 9-41, a CRF antagonist (p < 0.05, vs control). The pituitary GH levels were significantly elevated when intact and adrenoleutomised (ADX) rats were exposed to this hypoxia (p < 0.01, vs control). Pre-treating with either a high dose of dexamethasone (DEX) 500 ug ip, or low dose of DEX 199 ug ip, dropped the pituitary GH levels (p < 0.05, vs control). Hypoxia caused a evident increase in plasma PRL and not the pituitary PRL. ADX reduced pituitary PRL under hypoxia but the effects were reversed by pretreating with icv CRF antagonist and both low and high doses of ip DEX. When rats were pretreated with icv NE, hypoxia caused significant decreases in pituitary GH and increased plasma GH These effects were reversed by pretreating with icv yohimbine, an alpha-2 adrenergic receptor antagonist. When pretreated with icv Glu, hypoxia produced significant reductions in pituitary GH and increased pituitary PRL, these effects were reversed by icv AP-5, a NMDA receptor antagonist. These results may suggest that hypoxia suppresses body weight gain, which may be related to decreased release of GH. Hypoxia induces PRL release but inhibits GH secretion; hypothalamic CRF suppresses GH release but increases PRL release; central NE induces GH release through alpha-2 receptor affect; central Glu (by NMDA receptor) could stimulate GH secretion and suppress PRL in colchicines-treated rats under hypoxia.
HYPOXIA INDUCES ALTERATIONS OF THYROTROPIN-RELEASING HORMONE IN RAT HYPOTHALAMUS.

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This study examined the effects of 0.5h 2h, 24 h, 5 day, 10 day and 30 day exposure to hypoxia on TRH secretion from the median eminence (ME), response of TRH in paraventricular nucleus (PVN) of hypothalamus, and the modulation of norepinephrine (NE) on TRH in rats. The hypoxic stimulus occurred in a hypobaric chamber and a control group was at local altitude (2300m, 15.8%, O2). TRH levels were measured by specific radioimmunoassay. Hypoxia (5000m altitude, 10.8% O2) and severe hypoxia (7000m altitude, 8.2% O2) significantly enhanced TRH levels of ME and PVN and declined serum T3. Intraventricular injection of NE induced a decrease of TRH levels in ME and PVN (increased TRH release), and enhanced serum T3 at 7000m hypoxia for 2h. The stimulating effects of NE on TRH secretion could be abolished by icv yohimbine. We conclude that hypoxia exposure induces inhibition of hypothalamic TRH secretion from ME and PVN. Alpha-2-adrenergic receptors might play a role in the modulation of TRH release from the hypothalamus in acute hypoxia-exposed rats.

INTERMITTENT HYPOXIA INFLUENCES THE SECRETION OF PITUITARY GROWTH HORMONE AND THE GROWTH OF THE MALE RATS.

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We previously reported that repeated hypoxia suppressed body weight gains of rats and inhibited the growth hormone (GH) release from the pituitary. In order to understand the effects of intermittent hypoxia on changes of body weight and GH secretion, rats were exposed to hypoxia in a simulated hypobaric chamber, and the contents of GH in the pituitary were tested by immunohistochemistry. The data indicate that the rats’ weight gains were markedly suppressed from the 1st to the 11th day with intermittent hypoxia of 5 km altitude (10.8% O2) and began to regain hereafter. No alteration was found with intermittent hypoxia of 2 km altitude (16.0% O2, vs. control). GH contents were found to be 137.04% (P < 0.05 vs. control), 152.03% (P < 0.01 vs. control) and 138.94% (P < 0.05 vs. control) increase with intermittent hypoxia (2 km) for 5, 10 and 15 days respectively, and 188.43% (P < 0.01 vs. control), 346.18% (P < 0.001 vs. control) and 181.93% (P < 0.01 vs. control) increase with intermittent hypoxia (5 km) for 2, 5 and 10 days respectively. These results indicate that intermittent hypoxia significantly increases GH contents in the pituitary in rats depending on the time course and severity of hypoxia. Moderate intermittent hypoxia (5km altitude) suppress the growth of rats, which may relate to the reduced secretion of GH. The reduced GH release is due to hypoxia-activated SS release and SS mRNA expression.(we had published in Regulatory Peptides).

NEUROPEPTIDES AND HYPOXIC ADAPTATION.

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The responses to hypoxia of neuropeptides in the hypothalamus that regulate neuroendocrine behavior are important for deciphering mechanisms of adaptation to hypoxia. To explore the adaptive plasticity of the responses we applied a simulated altitude hypoxia in a hypobaric chamber. Our data show that the hypothalamic neuropeptides and immune system display adaptive plasticity in gene expression and peptide modulation in rats during acute and chronic hypoxia. Hypoxia depressed cellular immune activity and attenuated spleenocytes proliferation and DNA contents. This effect was mediated through NE. The parasympathetic system reduced hypoxia-suppressed immune responses. Intermittent hypoxia showed an elicited affect. Hypoxia suppressed humoral immune activity, reduced hemolysin formation and IgG production, that were modulated by Hypothalamic neuropeptides. Hypoxia-reduced humoral immune activity was modulated through hypoxia-activated HPA, stimulating hypothalamic CRF and NE that further suppressed immune function. β-EP involved in hypoxic down-regulation in humoral immune activity, T-lymphocyte DNA contents, hemolysin formation of SRBC-sensitized rat, and IgG level, acting through opiate receptor or possible sympathetic nervous system. AVP enhanced humoral immune response to hypoxia, increased hemolysin to SRBC and IgG production via V1 receptor in brain PVN. Supported by NSFC.no.30070289

INTERMITTENT HYPOXIA INFLUENCES THE SECRETION OF PITUITARY GROWTH HORMONE AND THE GROWTH OF THE MALE RATS.

Ji-Zeng Du1, Ning-Yi Xu1, Xue-Qun Chen1. Division of Neurobiology and Physiology, Zhejiang Univ (Yuquan campus), Hangzhou, China1. dujz@cls.zju.edu.cn.

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NEONATAL MATERNAL SEPARATION ENHANCES TIME-DEPENDENT PHRENIC RESPONSES TO HYPOXIA IN RATS.

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Neonatal maternal separation (NMS) is a stress that alters programming of the hypothalamo-pituitary-adrenal axis (HPAA) orchestrating the neuroendocrine responses to stress. Anatomical and functional evidence indicate that groups of HPAA neurones activated by stress modulate respiratory activity also. We recently showed that, in awake rats, the hypoxic ventilatory response of adult males (but not females) subjected to NMS is 25% greater than controls (Genest et al. 2002). To establish the effects of NMS on respiratory control development, and begin mechanistic investigation of NMS-related enhancement of the hypoxic ventilatory response, we tested the hypothesis that NMS augments time-dependent phrenic responses to hypoxia. Experiments were performed on two groups of male rats. Pups subjected to NMS were placed in a temperature controlled incubator 3h/day for 10 consecutive days (P3 to P12). Control pups were undisturbed. Once they reached adulthood (8 to 10 weeks), rats were anesthetized (urethane; 1.6g/kg), paralyzed, and ventilated with a hyperoxic gas mixture (FiO2 = 0.5). Rats were then exposed to moderate, followed by severe isocapnic hypoxia (FiO2 = 0.12; 0.08, respectively, 5-min each). NMS significantly enhanced both the frequency and amplitude components of the phrenic nerve response to hypoxia relative to controls. Upon return to hypoxia, post-hypoxia frequency decline was greater in NMS rats versus controls. We conclude that early life exposure to a non-pressor stress, such as disruption of mother-pup interactions, can affect development of the inspiratory (phrenic) response to hypoxia. This research was supported by the Hospital for Sick Children Foundation and CIHR.
**125. ANDEAN COMPARED WITH EUROPEAN WOMEN ARE PROTECTED FROM ALTIITUDE-ASSOCIATED INTRAUTERINE GROWTH RESTRICTION (IUGR).**

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Babies born at high altitude to long-term high-altitude residents weigh more than those of recent migrants from low altitude. **Objective:** We asked whether a gradient exists such that persons of Andean ancestry are protected relative to those of mestizo (“mixed”) and, in turn, European or other lowland ancestry. **Methods:** Medical records were examined from 3565 consecutive deliveries to women with ≥ 2 prenatal visits at public or private hospitals in Santa Cruz (500 m, low), Cochabamba (250 m, medium), and La Paz or Oruro (3600-3800 m, high). Population ancestry was judged by parental surnames. Persons of Bolivian nationality were assumed to have been born at their altitude of residence and non-Bolivians to have immigrated there as adults. IUGR was defined as birth weights <10th percentile for gestational age and sex using sea-level criteria. **Results:** Women were slightly older at high altitude but parity, number of prenatal visits, and pregnancy weight gain were similar. At high vs. low altitude, birth weight was lower (3011 ± 12 vs 3352 ± 15 gm, p < .01) but gestational age (38.8 ± 0.1 vs 38.9 ± 0.1 wk) and % pre-term deliveries (10.4 vs 8.8%) did not differ. IUGR babies were three times more frequent at high altitude (figure). The increase in IUGR was least in babies of Andean ancestry, intermediate in mestizos and greatest in Europeans. Within an ancestry group, there was no consistent birth weight difference between Bolivian vs. non-Bolivian nationals, suggesting that lifelong high-altitude residence had little effect. **Conclusions:** Andean ancestry protects against altitude-associated IUGR, suggesting the involvement of unknown genetic factors. (NIH TW01188, HL60131).

**127. RESPIRATORY EPITHELIAL ION TRANSPORT IS ALTERED AFTER 1 HOUR AT 4200M.**

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**Rationale:** Respiratory epithelial ion transport plays an important role in controlling extravascular lung water and is altered on ascent to high altitude. It can be assessed in vivo by measuring the transepithelial nasal potential difference (NPD). **Methods:** Measurements were made in 13 healthy subjects at sea level (SL) and after 1 and 6 hours (HA1 and HA6) of hypobaric hypoxia at an altitude of 4200m. NPD was measured during perfusion of the nose with 154mM NaCl at SL, HA1 and HA6, and with NaCl 10^{-4} M amiloride; low Cl^{-} solution 10^{-4} M amiloride, and low Cl^{-} 10^{-5} M Misoprenaline, at SL and HA6. **Results:** Ascent to 4200m resulted in a hyperpolarization in the basal NPD at HA1 and HA6 and an increase in the amiloride inhibitable portion (Δ Amiloride) of the NPD at HA6. Stimulated CI^{-} transport with low Cl^{-} or isoprenaline was not significantly altered. **Conclusions:** The change in NPD after only 1 hour is too rapid to be due to changes in channel synthesis and suggests that hypoxia affects the conductance, open probability or trafficking of respiratory epithelial ion channels.

**128. COPING WITH HYPOXIA: ELITE CLIMBERS.**

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The purpose of this study was to explore the mental strategies used by successful Everest climbers, to overcome obstacles (hypoxia) while climbing Mount Everest. A group of elite climbers (n = 9) were interviewed in order to assess the mental strategies used by them to overcome obstacles while attempting a successful climb of Mount Everest. In-depth interviews were conducted with 9 elite climbers who succeeded (at least once) in reaching the summit of Mount Everest. An inductive analysis of the data revealed that the mental strategies used to overcome obstacles included: disassociation, teamwork, self-confidence, focus and short-term goal setting. Mental training is an essential part of training in preparation for coping with obstacles (hypoxia) that may prevent climbers from successfully summiting high mountains. This study shows that mental training is a useful tool in helping climbers cope with hypoxia.

**129. SUBLINGUAL GLYCERYL TRINITRATE INDUCED HEADACHE AS A PREDICTOR FOR INCipient ACUTE MOUNTAIN SICKNESS.**

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The most common symptom associated with Acute Mountain Sickness (AMS) is headache. The headache may be caused by meningeal irritation as a result of blood vessel dilatation. Glycerine trinitrate (GTN) is known to dilate cerebral vasculature and causes headaches similar in quality to the headache associated with AMS. This study evaluated the relationship between GTN induced headache and AMS scores. Subjects were recruited from two separate expeditions to Kilimanjaro (5892m) and Pk6175 (6175m) in the Indian Himalaya comprising nine and six healthy adult volunteers respectively. Headache shift vectors (HSV) were calculated from headache scores rated pre and post sub-lingual GTN administration. Baseline HSSs were calculated for each subject at sea-level. GTN induced headache shifts were rated daily on ascent to altitude and by subtracting baseline observations normalised HSSs (nHSV) were calculated. The data was analysed using the Fisher test. A positive correlation was found between nHSV and change in the observed AMS scores (ΔAMS) over the following 24 hours where a further ascent of between 400–1000m occurred (Kilimanjaro - p = 0.003; Pk6175 – p = 0.005). The relative risk of developing a large shift in AMS score (ΔAMS) given a high headache shift vector (nHSV) was found to be 5.42 and 3.71 for the Kilimanjaro and Pk6175 groups respectively. These findings support the hypothesis that sublingual GTN may be useful as a predictor for incipient AMS.
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